<u>**Final Progress Report**</u>

HIV/HCV Support Team to Improve Medication Safety and Engagement in Care

Principal Investigator: Stephen A. Berry, MD, PhD

Team Members: David Thompson, PhD; Elizabeth Holmes, RN; Janessa M. Smith, PharmD; Andrea Ciaranello, MD, MPH; Thomas Grader Beck, MD, PhD; Fidelia Bernice, PharmD; Kelly A. Gebo, MD, MPH; Walid El-Nahal, MD

Organization: Johns Hopkins University School of Medicine

<u>**Abstract**</u>

Purpose: The project assessed whether a hospital-based nurse and pharmacist human immunodeficiency virus/ hepatitis C virus (HIV/HCV) support team (HST) could reduce inpatient medication errors and improve engagement in outpatient HIV care for persons living with HIV (PLWH).

Scope: Adults hospitalized at the Johns Hopkins Hospital, 2017-2019.

Methods: Phased, cluster-randomized trial with co-primary outcomes of 1) HIV medication errors and 2) achieving HIV viral suppression within 6 months of discharge among PLWH without viral suppression on admission.

Results: Among the 697 hospitalizations involving antiretroviral prescriptions, only three involved incomplete HIV regimen errors, historically a common and highly consequential error type. Among 109 PLWH not virally suppressed on admission, 24 of 57 (42%) control and 23 of 52 (44%) intervention hospitalizations were followed by viral suppression within 6 months (p=0.49).

Our results reflect a national shift to simpler, safer HIV regimens and indicate the HST was not effective at increasing post-discharge care engagement. The project results help demonstrate major changes in the field of HIV medicine, including a dramatic shift toward single-tablet regimens, with extremely low rates of side effects and drug interactions and a progressive (and highly desirable) shift toward more PLWH coming into care and achieving viral suppression on these regimens. Therefore, the project team discontinued plans for an online HST toolkit and for a cost-effectiveness analysis.

However, the study's electronic medical record (EMR) alert for PLWH was 100% sensitive (82%-100%), with a PPV of 83% (81%-85%). The EMR alert that facilitated our interventional study is novel and was successful, and we have submitted results of an analysis of its accuracy as well as a description of lessons learned in the process of creating it. The project team has also implemented and started to evaluate a similar alert for HCV.

Key Words: HIV medication errors, engagement in HIV care, EMR alert

Purpose

Original Aims:
1. Implement a human immunodeficiency virus/hepatitis C virus (HIV/HCV) support team (HST) as a quality improvement intervention at Johns Hopkins Hospital in Baltimore, MD. The project used a phased, cluster-randomized, roll-out, stepped-wedge study to assess whether the HST decreases HIV and HCV medication errors and improves HIV linkage and re-engagement in care.

2. Develop a toolkit for non-HIV/HCV expert nurses and clinical pharmacists to learn and perform/enact the HST roles and an implementation strategy for hospitals.

3. Use the Cost-Effectiveness of Preventing AIDS Complications model to project the HIV-related clinical outcomes, costs, and cost-effectiveness of the HST intervention.

Additional Aim:
1. Develop and assess the accuracy of an electronic medical record (EMR) alert to identify hospitalized persons who have untreated HCV.

Scope

In 2014, the 1.3 million persons living with HIV (PLWH) in the US had approximately 250,000 hospitalizations. Their all-cause hospitalization rate was two to four times higher than among the general population ages 18-65 years old (JAIDS 2012). Starting in 1996, use of combination antiretroviral therapy (ART) among PLWH led to a sharp decline in HIV-related mortality and morbidity, including hospitalizations (NEJM 1998). During 2000-2010, however, there was a leveling in the rate of hospitalizations. Increases in hospitalizations due to end-organ (cardiovascular, hepatic, renal) diseases were observed in some settings (JAIDS 2012). With the prevalence of PLWH increasing by 30,000 annually and the median age of PLWH now at 50 years old and increasing (CDC HIV Surveillance 2011), the absolute number of hospitalizations may increase in coming years.

Antiretroviral treatment (ART) transforms HIV from a terminal condition to a chronic comorbidity with a nearly normal life expectancy (PLoS One 2013). Current ART regimens are safer than regimens of the early 2000s and often have only one to five pills per day. From a societal perspective, it has become clear that viral suppression with ART decreases HIV transmission by over 95% (NEJM 2011). In the setting of high uptake and adherence, ART has the capacity to diminish or halt the epidemic (Lancet 2009). US guidelines now recommend ART from the time of HIV diagnosis (DHHS Guidelines 2013), and, as of 2013, approximately 400,000 PLWH (33%) were using it (JAMA Int Med 2013). Errors involving ART previously happened during 20% to 40% of hospitalizations in which they were prescribed (10% to 20% of all HIV hospitalizations), despite current, relatively simple regimens and despite decision support tools contained in electronic order systems (Clin Infect Dis 2012). Errors may be categorized as in Table 1.

Table 1. Categories of ART Errors with Examples

Category	Inpatient Order	Error and Potential Consequences
Incorrect dose/ schedule	Abacavir 300 mg and lamivudine 300 mg once daily despite outpatient use of Epzicom (abacavir 600 mg/lamivudine 300 mg) once daily	Hospital substitution of component generics for branded Epzicom is complicated by no existence of abacavir 600 mg standalone tab. Subtherapeutic abacavir results in viral rebound and lamivudine resistance.
Incomplete regimen	Darunavir, raltegravir, and Truvada (emtricitabine/tenofovir) as only meds	Ritonavir **not** ordered, resulting in subtherapeutic darunavir levels, viral rebound, and acquisition of emtricitabine and raltegravir resistance.
Contraindicated combination	Midazolam sedation for an endoscopy despite ritonavir use	Inhibition of hepatic midazolam clearance by ritonavir increases midazolam levels and half-life, resulting in multiday coma.
Unknown toxic potential	Truvada (emtricitabine/tenofovir) maintained despite acute renal failure	Tenofovir is renally cleared and is nephrotoxic at supratherapeutic levels, resulting in compounded renal failure.

Many ART agents interact with other drugs. The most important example is the pharmacologic booster ritonavir, which was part of >50% of regimens during hospitalizations during 2000 to 2010 (Ann Pharmacother 2008). Ritonavir inhibits cytochrome p450 and other hepatic pathways and, consequently, has complex and often dangerous interactions with glucocorticoids, opioids, calcium channel blockers, statins, antiarrhythmics, and other agents.

Incomplete regimen errors are common and have dangerous consequences that are unique to HIV. Incomplete regimens may occur in over half of instances (Clin Infect Dis 2012). PLWH often cannot name their ART medications and doses (JAIDS 2001). Low health literacy and polypharmacy are compounding problems for many PLWH (AIDS Care 2005). The challenge to non-HIV specialist providers is also clear. Generalist physicians answered 35% of ART knowledge questions correctly compared with >90% among infectious disease (ID) physicians in a recent survey (J Int AIDS Soc 2009). Knowing what constitutes a full regimen is made more difficult by combination tablets, boosting agents, and the complicated regimens used in cases of extensive resistance.

Viral rebound with acquisition of medication resistance is the most important complication of incomplete regimens. Rebound and development of resistance often occur by 7 to 14 days (AIDS 2008). In one academic hospital, a median of 3.5 days (IQR 3-5) passed before discharge (which could include propagation of the error in discharge instructions) or correction of the error by the hospital team (Am J Health Syst Pharm 2007). Post-discharge outpatient HIV follow-up visits occur about 2/3 of the time but typically occur 7 to 14 days after discharge (AIDS 2013). Thus, adverse effects are likely to occur before an outpatient HIV provider can correct the error. Ultimately, viral resistance can lead to immune dysfunction and death if new, successful ART is not initiated.

Electronic decision support tools are limited in their ability to prevent ART errors (Clin Pharmacol Ther 2008). Reasons include provider fatigue with warnings and inability to keep tools updated (Clin Pharmacol Ther 2008). Despite universal electronic decision support at our hospital, ART errors occurred in 30% of hospitalizations involving ART (Clin Infect Dis 2012). One tool recently developed and optimized by HIV researchers was able to demonstrate a 35% reduction in ART errors (ID Week 2013).

Since 2011, hepatitis C virus (HCV) therapy has undergone a revolution similar to that of HIV therapy in 1996. Cure rates have increased from 30% to >90% (NEJM 2014). About 3 million Americans are living with HCV (NEJM 2013). More annual deaths are now attributable to HCV through cirrhosis and liver cancer than are attributable to HIV/AIDS (Ann Intern Med 2012). The roll-out of HCV therapy has been limited by several issues, including cost, with a treatment course previously priced around $150,000 (Hepatology 2014).

Despite the cost, HCV treatment is a public health priority, and up to a million Americans may be treated in the next decade (Ann Intern Med 2014). Treatment lasts only 3 to 6 months. However, many hospitalizations during treatment may be expected because of the absolute number of people being treated, the median age of 50 years old (Ann Intern Med 2014), and the frequent comorbidities among this population (BMC Infect Dis 2012). Because of shared transmission routes, the HCV epidemic overlaps closely with the HIV epidemic; 38% of PLWH hospitalized at our institution have HCV, and this is likely representative of many urban hospitals.

HCV antivirals are used in two to three drug regimens and, similar to ART, there are multiple ways in which dangerous inpatient medication errors may occur. Between 2011 and 2016, seven drugs became available (NEJM 2014). Like with HIV ART, there are complex drug interactions and dose adjustments (Dig Liver Dis 2013). Prescribing incomplete regimens may be common for the same reasons as for ART (lack of knowledge of the drugs, ineffectiveness of decision support tools). The consequences of incomplete HCV regimens also mirror those for ART. HCV viral rebound may occur quickly. In a recent case at Hopkins Hospital, rebound occurred after 6 days of an incomplete regimen. Rebound may lead to drug resistance, and, even when it does not, it necessitates restarting the treatment course. With a $150,000 price, preventing re-treatment is critical.

Engagement in Outpatient HIV Care

As of 2011, the large proportion (two thirds) of US PLWH who were not using ART represented a health system crisis, given ART's transformative potential and low risk. ART cannot be prescribed and safely monitored without regular engagement (follow-up) in outpatient HIV care. Helping PLWH "link" to care (make a first HIV provider visit) and then remain engaged are major obstacles to increasing ART use. The continuum of HIV care (Figure 1) from initial infection to suppression with ART has large stepdowns at the point of linkage (about 77% of persons ever diagnosed are linked) and at consistent engagement (about 66% of persons linked are "retained"). Improving linkage and retention have been set as a top national HIV priority by DHHS (HHS strategic plan, accessed 09/25/14).

Figure 1. HIV Care Continuum in the United States
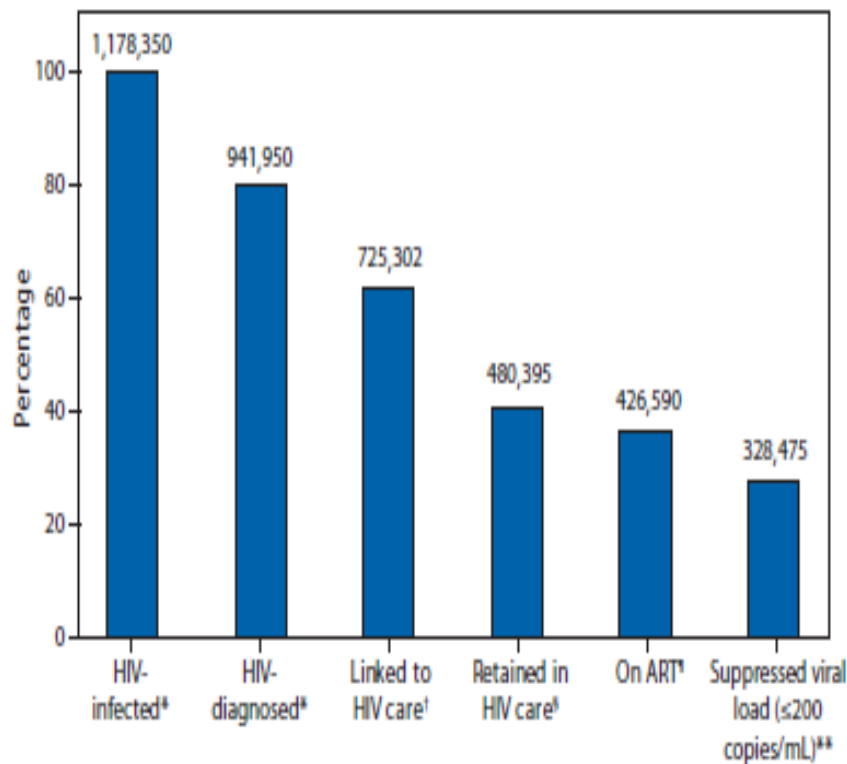
MMWR 2011;60(47):1618-23

Hospitalizations represent critical opportunities to improve linkage. HIV testing and diagnosis often occur during hospitalization because of either indicative findings or screening. Following diagnosis in hospitals and emergency departments (EDs), only 50% to 60% of persons link to care (Acad Emerg Med 2012). There are probably many reasons for this, including denial, stigma, distrust, and practical difficulties (such as with insurance, transportation, and homelessness) (AIDS Patient Care STDS 2012). Studies of HIV-expert nurse and social worker interventions have demonstrated improvement in ED linkage up to 90% (AIDS Patient Care STDS 2011). Intervention components have included education by a knowledgeable counselor, addressing insurance and transportation needs, scheduling a visit within a few days, making a "warm" handoff by naming or introducing HIV clinic staff, and performing phone follow-up (AIDS Patient Care STDS 2012). Many HIV clinics can see uninsured new patients by establishing emergency Ryan White HIV/AIDS Program coverage (supplemental federal assistance for low-income PLWH) with a turnaround of 24 or fewer hours. There are few data on interventions to improve retention (Clin Infect Dis 2014), and we are not aware of literature reporting the rate of re-engagement (lost to follow-up patients returning to care at a prior or new HIV clinic) following a hospitalization. Persons who are lost to follow-up almost always are not taking ART and have uncontrolled HIV replication (CROI 2014).

A minority of hospitals account for a high volume of hospitalizations of PLWH. In eight states (FL, GA, LA, MA, MO, TN, VA, and WA) that are reporting all 2011 non-federal hospitalizations to AHRQ's State Inpatient Database, 28,971 (51%) of a total of 56,794 hospitalizations of PLWH occurred in just 53 (4%) of 1,467 total hospitals (personal communication, John Fleishman, PhD, at AHRQ). Such aggregation of hospitalizations might be expected, given that HIV prevalence is also concentrated in certain, mostly urban, locations (CDC HIV Surveillance 2011). Each of these 53 hospitals had >250 hospitalizations of PLWH. Twenty hospitals each had >500 hospitalizations. Extrapolating upward to the national level based on the share of all PLWH living in these eight states suggests approximately 210 hospitals with >250 annual hospitalizations (CDC, State HIV prevention progress report 2014). An intervention to decrease HIV and HCV medication errors and to improve outpatient engagement of PLWH may be critical for such high-volume centers.

An optimal intervention would be scalable to a hospital's volume of hospitalizations of PLWH, would be implementable using care providers already working at the hospital, and would be cost-effective.

An intervention consisting of a part-time role for an experienced RN-level inpatient nurse would be scalable in that increments of effort may be devoted as required. A hospital with <250 hospitalizations of PLWH may use a small increment (e.g., 25%). RN-level inpatient nurses are available in every acute care hospital in the US. Clinical pharmacists who could be trained in HIV and HCV medications are also commonly available. There are limited data on the cost and cost-effectiveness of linkage and re-engagement strategies. New patient counseling by an outpatient HIV case manager had an average cost of $790 per patient and was associated with an increase in 3-month linkage from 60% to 87%. Using an HIV progression and transmission model, CDC investigators estimated an incremental cost-effectiveness ratio of $62,200 per quality adjusted life year (QALY) gained, a result considered cost effective based on a commonly accepted willingness-to-pay threshold of $100,000 per QALY (JAIDS 2012). The study considered only one generation of potential HIV transmission from index patients. Another study found that a theoretical increase in the rate of viral suppression from 80% to 90%, brought about primarily through improving retention in care, would be associated with an 11% reduction in HIV incidence nationally (PLoS One 2012).

HIV disproportionately affects minority and underrepresented population groups; 54% of PLWH are men having sex with men (MSM), 46% are African American, and 17% are Hispanic (MMWR 2011). Over 80% of persons diagnosed with AIDS live in urban areas (CDC HIV/AIDS Surveillance Supplemental Report 2008), and 44% of persons receiving HIV medical care have income at or below the federal poverty limit (MMWR 2014).

Pilot Data from the Johns Hopkins Hospital HIV-specialty unit

This study's intervention was based on activities that have been performed since approximately 2002 on the 18-bed HIV-specialty unit of Johns Hopkins Hospital. There, an HIV-specialist nurse had a dedicated time for case management, often focused on linkage and re-engagement. An HIV-specialized clinical pharmacist reviews medication for all patients each day. In 2013, 927 (58%) of 1,609 total hospitalizations of PLWH at Hopkins Hospital occurred on the HIV/AIDS unit.

Members of our team published an analysis of the effect of this medication review for 380 hospitalizations in 2009, all of which included ART orders on hospital day 1 (Clin Infect Dis 2012). A total of 145 ART errors occurred in 110 (29%) hospitalizations. After the first day of pharmacist review, 133 (92%) errors were eliminated, leaving only 12 hospitalizations (89% reduction) with persisting errors. All incomplete regimen errors were eliminated.

The project team generated hypotheses about the potential effects of nurse-led linkage and re-engagement efforts from previous work in the Hopkins ED and on the HIV-specialty unit. A nurse-led program in the Hopkins ED included a clinic nurse visit to the ED and/or next-day phone call, a nurse/social worker appointment within 48 hours, HIV peer counseling, baseline lab work, establishment of Ryan White HIV/AIDS Program coverage if uninsured, provision of a taxi voucher if needed, and appointment reminder calls. As of 2013, the program achieved a 90% 30-day linkage rate, up from a historical rate of 54% (Acad Emerg Med 2012). In parallel fashion, the HIV-specialty unit care coordination nurses attempt to re-engage persons lost to outpatient follow-up. The nurses assess reasons, contact the provider, counsel the patient, provide an expedited appointment, and help with Ryan White coverage and transportation. A review of 175 hospitalizations of PLWH who were lost to follow-up revealed 63% re-engagement among patients discharged from the HIV-specialty unit at Hopkins Hospital versus 22% for discharges from other units.

<u>Methods</u>

Aim 1: Implement an HIV/HCV Support Team (HST) as a quality improvement intervention at Johns Hopkins Hospital in Baltimore, MD. Using a phased, cluster-randomized roll-out (stepped-wedge study), assess whether the HST decreases HIV and HCV medication errors and improves HIV linkage and re-engagement in care.
The intervention is composed of the availability of an HIV Support Team (HST), consisting of a nurse (50% effort) and a clinical pharmacist (10% effort). The team saw patients on non-holiday weekdays. The HST nurse's training was to serve a double purpose in being part of toolkit (Aim 2) generation. The HST clinical pharmacist role was to be an extension of current duties for an HIV-specialty pharmacist.

Overall, the HST was a resource a regarding HIV and HCV medications and would assist in the transition to outpatient care for many PLWH. The HST would not provide diagnostic advice and will not replace the Infectious Diseases consultative team. Linkage pertains only to PLWH who have never had an outpatient HIV appointment and is defined as keeping an HIV outpatient appointment within 30 days of discharge. Re-engagement pertains only to previously linked-to-care PLWH who have not kept an outpatient HIV appointment within a year prior to admission and is defined as keeping an HIV outpatient appointment (previous or new provider) within 30 days.

All hospitalized PLWH were briefly evaluated by the HST nurse. Per current hospitalization rates, the expectation was that there would be an average of 2.5 new patients per workday, including weekend admissions being met on Monday. All PLWH on ART received medication reviews throughout their hospitalization. All unlinked-to-care PLWH (including new hospital diagnoses) and all PLWH out of care for over a year would receive linkage/ re-engagement activities. Persons with HCV monoinfection would be seen only if they were taking HCV antivirals at the time of admission; they received daily medication review. See Table 2 for a description of the HST nurse daily schedule.

Table 2. Typical HST Nurse Daily Schedule

08:00-09:00	Assemble patient list. Meet new patients, call outpatient pharmacies and HIV providers.
09:00-11:00	For linking/re-engaging patients, speak with primary teams about medical and discharge plans. Patient and family education and outpatient care coordination for linkage/re-engagement.
11:00-12:00	Medication review together with clinical pharmacist, help communicate recommendations to teams

The HST received **automated, electronic notifications** of new patients via custom Epic™ software tools, which are triggered by first-within-the-hospitalization orders for HIV or HCV medications or when any positive HIV antibody test, CD4 count, or HIV viral load (HIV RNA) laboratory assay is resulted.

Medication reviews would begin with the HST nurse independently ascertaining the outpatient HIV and/or HCV medication regimen on the first day. The HST nurse interviewed patients and/or caretakers and called the outpatient pharmacy and outpatient physician's offices.

The nurse and the HST pharmacist then assessed the inpatient orders and advise the primary team on the fidelity to the outpatient regimen, potential drug toxicities, and on any contraindicated drug combinations, considering all inpatient medications. On all subsequent hospital days, the HST pharmacist reviewed for new contraindicated combinations and would review renal and liver laboratory tests when relevant.

For patients continued on outpatient HIV medicines but determined during their inpatient stay to have detectable (>400 copies/mL) HIV RNA, the HST assisted the inpatient team in communicating with the outpatient HIV provider in deciding whether to remain on the regimen, change the regimen, or discontinue HIV medications until outpatient follow-up.

Linkage and re-engagement activities were be carried out by the HST nurse for appropriate patients, as shown in Table 3. Patient education centered on helping patients engage in learning about HIV and explore facilitators and barriers to their own care.

Table 3. Linkage/Re-engagement Activities

Patient Learning

<u>Active Learning</u>: Teach-back method

<u>Family/Caregivers</u>: encourage participation; respect that some patients keep HIV confidential

<u>Starting Point</u>: assess baseline HIV knowledge, assess fears (e.g., conspiracies, Rx side effects)

<u>Facilitators and Barriers</u>: motivational interviewing. An example facilitator is a friend; barriers may be transportation, substance abuse.

<u>Peers</u>: Hopkins HIV clinic-based peer advocates will come to bedside

Connection to Outpatient

<u>Provider Contact</u>: encourage visits from new (or previous) outpatient MD, RN, case manager

<u>Tour Clinic</u>: physically permitting, walk new patients to Hopkins Hospital HIV clinic

<u>30-Day Appointments</u>: provide scheduled appointments ASAP; use established outpatient clinic contacts when possible

Psychosocial Needs

<u>Assess Social Needs</u>: advise unit case managers about HIV-specialty services (e.g., Ryan White insurance, AIDS Drug Assistance Programs)
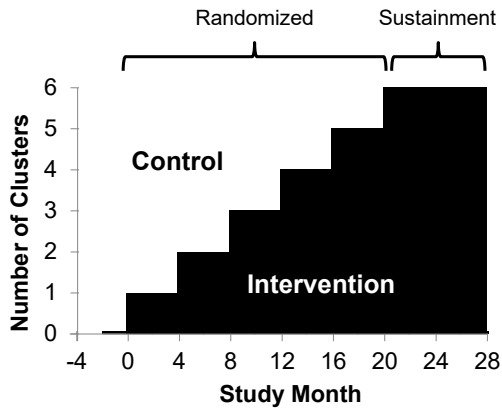
<u>Co-located Mental Health</u>: refer patients in need to HIV clinics with onsite substance abuse and mental health services

Post-Discharge

<u>Appt Reminder</u>: call all linking/re-engaging patients

<u>Available</u>: for direct incoming calls

Study Setting, Design, and Duration

The phased roll-out was designed to allow the HST RN to gain efficiency. The design also allowed an opportunity to compare randomly allocated control and intervention groups.

Because of our prior expectation that the medication review would likely benefit patients, the design was favorable to a parallel design, in which certain units would never receive the intervention, and to a crossover design, in which the intervention would be removed after a period of time.

Data Collection and Ascertainment of Outcomes

Data necessary to assess the HST program's efficacy (Table 4) were collected through manual chart abstraction by trained abstractors. These data included demographics, hospitalization characteristics, and in-hospital lab results. Post-discharge outpatient visits and HIV RNA lab results were also collected for a subset of patients.

Data analysts masked to control vs. intervention status ascertained outcomes, including HIV and HCV medication errors and linkage and re-engagement. Medication errors were classified as in Table 1.

The study took take place on 54 Johns Hopkins Hospital adult services other than the HIV specialty service. As above, about half of admissions of PLWH to Hopkins Hospital historically occurred on the HIV specialty service, with the rest scattered across 54 other services. The study was planned to have a 24-month phased roll-out (also called stepped-wedge).[104] Prior to roll-out, the 54 hospital units were randomly assigned into six clusters (8-10 units each) balanced with respect to three variables: 1) annual HIV admission volume, 2) medical vs. surgical, and 3) intensive care vs. floor. Every 4 months during roll-out, an additional cluster was randomly selected to join the intervention group. All clusters would have the intervention by month 20 (see Figure).

Table 4. Aim 1 Study Variables

HIV status	ICD-9 (or -10) discharge diagnosis code
HCV Rx use	Per medication list review
Hospital unit(s)	Admitting and discharging units among 53 possible
Length of stay, discharge status	Status includes alive/deceased, transfer
Readmissions	Within 30- and 180-day windows
Demographics	Age, gender, race, insurance
HIV-risk factor(s)	Injection drug use, male/male sex, heterosexual, vertical transmission, blood product, or other
CD4, HIV RNA	Results nearest admission date but prior to discharge
Inpatient medications	Ordered: All hospital days up through 14 and discharge summary
Follow-up visits	30-, 180-day kept HIV appointments
Follow-up HIV RNA	All values within 180 days
Follow-up HCV Rx	Completed vs. restarted course, virologic outcome

Analytic Plan

Hypothesis 1A: The HST will reduce HIV and HCV medication errors by at least 75%.

The primary analysis compared the proportion of hospitalizations with any HIV medication error present on the second day of HST availability (weekends and holidays are unavailable days) between units randomized to either control or intervention during roll-out.

Our preliminary work found that nurse/pharmacist review reduces the number of hospitalizations with any HIV medication error, persisting to the second hospital day, by 89%. We conservatively hypothesized a 75% reduction to account for delays from the HST communicating with multiple teams on multiple floors.

Analysis included multivariate logistic models to adjust for potential confounders and to assess associated factors, including demographics, insurance, CD4, HIV RNA, and type of ART regimen.

Models account for within-unit and within-person correlation. Secondary analyses examined incomplete regimen errors and any-type errors on the day of discharge. Analyses for HCV medication errors were parallel to those for HIV.

Hypothesis 1B: For patients unlinked to outpatient HIV care, the HST will increase 30-day post-discharge linkage to 90%; for patients lost to outpatient HIV follow-up, it will increase 30-day re-engagement to 60%.

Primary analyses of both linkage and re-engagement was performed similar to the analysis of medication errors. Secondary analyses examined virologic suppression at 180 days following discharge.

Sample Size and Power

For HIV medication errors, the sample was the fraction (54% in our preliminary work) of hospitalizations with HIV medication prescription on hospital day 1.

Based on data from 2009-2013 showing approximately 700 annual PLWH hospitalizations to the study services, and having 10 calendar months in both intervention and control, the project team expected the N for both intervention and control to be 315 hospitalizations.

From 9/1/2013 to 8/31/2014, there were approximately 100 hospitalizations with HCV medication orders among the 54 units. We conservatively expected 200 annual hospitalizations by 2016 with the expansion of HCV treatment. For 10 control and intervention months, the sample thus would be 170. The estimated samples for linkage were 108 control and 108 intervention.

The estimated sample for re-engagement was 23 control and 23 intervention. This is based on Hopkins HIV cohort data in 2006-2011 on the frequency of hospitalizations among persons disengaged for at least a year. Power calculations are described in Table 5.

Table 5. Power Calculations (α=0.05 for all calculations; most done with the *clustersampsi* add-in to Stata)

	Control hosps with event	Detectable alternative	Intervention hosps with event	**Power**
Hypothesis 1A				
HIV Rx errors (all)	91 (29% of 315)	50% reduction[A]	45	0.98
HIV Rx errors (incomplete regimen)	47 (15% of 315)	67% reduction[A]	15	0.98
HCV Rx errors (all)	49 (29% of 170)	50% reduction[B]	24	0.88
HCV Rx errors (incomplete regimen)	25 (15% of 170)	67% reduction[B]	8	0.85
Hypothesis 1B				
Linkage	58	54% control vs. 80% intervention[C]	87	0.90
Re-engagement	5	22% control vs. 60% intervention[D]	14	0.67[E]

A. Control rate for HIV Rx errors (all and incomplete regimen) based on preliminary data from the HIV/AIDS unit. The detectable alternative from these data was 75% reduction. However, we conservatively use 50% for all errors and 67% for incomplete regimen errors as still-clinically-meaningful minimum alternatives.

B. Control rate of HCV Rx errors (all and incomplete regimen) and detectable alternative extrapolated from HIV Rx rate.

C. Proportions based on Hopkins Hospital HIV clinic/Hopkins ER intervention (personal communication, Richard Rothman, MD).

D. Based on review of 175 hospitalizations at Johns Hopkins Hospital occurring to out-of-care PLWH.

E. Power for Fisher's exact test; because only about half an even per unit is expected, very little overdispersion, if any, can be expressed; calculated using PS Software, http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize.

Aim 2: Develop a toolkit for non-HIV/HCV expert nurses and clinical pharmacists to learn and perform the HST roles and an implementation strategy for hospitals.

The toolkit included 1) curriculum for training an HST nurse, 2) protocols for HST nurse activities, 3) curriculum for training an HST clinical pharmacist, 4) protocols for the medication reviews, and 5) an implementation strategy that hospitals can use to establish an HST program.

Dr. Thompson led toolkit development, using an iterative approach similar to the process used for previous toolkits. In the year before the intervention roll-out, Drs. Thompson and Berry followed a peer assessment model used by the World Association of Nuclear Operations to systematically assess current activities of the HIV/AIDS unit care coordination nurses (Am J Med Qual 2012).

Using this model, a list of activities was developed and reviewed to assess where improvements could be made. All activities related to the following tasks were identified: 1) ascertaining outpatient HIV and/or HCV regimens, 2) assisting the clinical pharmacist in medication review and communicating to the primary inpatient team, 3) engaging newly diagnosed or currently lost-to-follow-up patients in learning about HIV and about its medical management, 4) assessing barriers to consistent outpatient care and potential social needs, and 5) assisting in overcoming these barriers and in keeping a post-discharge HIV follow-up visit.

An initial summary of these activities is described above. Formal review was conducted more comprehensively in the first year of the project. The project team used a contextual inquiry to assess the rationale for all activities, as was done for previous projects (Ergonomics 2013). The plan was to also assess the efficacy of currently used tools, such as medication reconciliation sheets, patient risk assessment forms, and patient educational handouts. The project team's systematic assessment informed development of an initial set of HST nurse curriculum and HST nurse protocol toolkit materials. The curriculum materials were used to train the HST nurse prior to the intervention roll-out to ensure understanding of HIV and HCV regimens and HIV prognosis, linkage, and re-engagement.

The curriculum included didactic modules, similar to those used for central line infections (www.hopkinsmedicine.org/armstrong_institute/improvement_projects/stop_bsi/clabsi_toolkit.html). A quiz was administered upon completion of the modules, with an 85% required for a passing score. The initial nurse protocol materials included a list of all usual activities for an HST nurse, a checklist of tasks that can be customized for each patient, and a list of specific tools developed for the project.

The HST nurse had the following training support: 1) shadowing the care coordination nurses on the HIV/AIDS service; 2) advice from an HST Nurse Advisory Panel, consisting of the care coordination nurses (Debbie Michell, RN, and Lisa Wolf, RN, MSN), and from the HIV/AIDS unit social worker (Jennifer Maurer, LCSW); and 3) individual instruction from HIV expert physicians and pharmacists.

The shadowing was kept short---at 2 to 3 days---a duration believed realistic because nurses in other settings may travel for a limited time to different hospitals to learn an HST role. Goal setting for learning from the shadowing was guided by an existing shadowing tool developed by Dr. Thompson (TJC Journal on Quality and Patient Safety 2008).

At the end of roll-out and during sustainment, the nurse-related portions of the toolkit were be revised based on Dr. Thompson's and Dr. Berry's repeated systematic assessments of daily activities, direct input from the HST nurse, and advice from the HST Nurse Advisory Panel.

A current HIV pharmacist took on the role of HST clinical pharmacist as an extension of current work in the same capacity on the HIV/AIDS unit. During roll-out months 4 to 9, when the volume was relatively light, Drs. Thompson and Berry systematically assessed her activities. The HIV pharmacist's direct input was sought in the initial development of the clinical pharmacist portions of the toolkit.

The HIV pharmacist's activities were observed again during the sustainment phase (full patient load) to inform revision of the toolkit materials. The toolkit materials included training modules and quizzes related to HIV and HCV medications. The modules and quizzes were piloted on clinical pharmacist residents.

Aim 3: Use the Cost-Effectiveness of Preventing AIDS Complications model to project the HIV-related clinical outcomes, costs, and cost-effectiveness of the HST intervention.

Hypothesis 3: The HST will prevent HIV disease outcomes and secondary HIV transmission, rendering it a cost-effective intervention in settings with moderate or high HIV prevalence.

For this aim, the plan was to focus on identifying the long-term clinical outcomes, costs, and cost-effectiveness of an HST program. How is the value of an HST program altered by HIV prevalence among inpatients; by HST linkage and re-engagement effectiveness, durability, and cost; and by other key factors related to HIV care, such as viral suppression rates and transmission rates?

Population and intervention:

The project team planned to define a population of hospitalized PLWH, with specified age, gender, HIV risk group, CD4, and viral load characteristics. We compared a cohort of patients who receive HST services with a cohort not receiving these services. The project team examined medication safety and linkage and re-engagement. All patients, regardless of HST receipt, still faced risks of loss to follow-up after a kept appointment, ART failure, and other features of routine HIV care.

Data sources:

Aim 1 study data comprised the primary source for baseline cohort characteristics and HST effectiveness data. HST costs were estimated from HST implementation and included the training costs and salaries of HST personnel and management-level salary to oversee implementation (estimated from investigator time). The project team included viral suppression rates at 6 months after discharge (if insufficient study data, published values would

be used instead for the project [Am J Epidemiol 2003]). Additional clinical data needed for the CEPAC model were derived from the published literature; see Table 6.

Model outcomes:

As indicated in Table 6, the project team projected key outcomes, including clinical events and costs. We first simulated short-term, 6-month outcomes---including ART toxicity, resistance, and viral rebound---validating the model by ensuring that results match observed trial data. Next, we projected long-term outcomes.

The costs associated with the clinical events, in particular transmission to partners, may partially or fully offset the cost of the HST program, making it an excellent value from the healthcare system perspective.

Table 6. Selected Data Parameters and Outcomes for CEPAC Model-based Analysis of HST Program

Data from the HST study

Parameter	Short-term outcomes	Long-term outcomes
Medication error	ART toxicity	Switch to next line of ART (more costly, greater pill burden, risk of *reduced ART adherence*), "exhaust" one available ART regimen Morbidity, mortality, costs related to toxicity
	ART resistance	Switch to next line of ART, next line may be less efficacious, more costly
	Increase in HIV RNA	Increase transmission to partners, CD4 decline, morbidity, mortality, costs
No linkage to care	HIV disease progression	HIV transmission to partners due to unsuppressed HIV RNA
No re-engagement	HIV disease progression	HIV transmission to partners due to unsuppressed HIV RNA

Additional key parameters from published literature

  Viral suppression rates for six successive lines of HIV regimens; CD4 gain on ART; CD4 decline off ART
  Opportunistic infection and mortality rates (by CD4 and ART use)
  HIV transmission to partners (a function of HIV RNA level)
  HIV care costs (inpatient care, outpatient care, medications, laboratory studies)
  Hospital-level factors: HIV prevalence among inpatients, training costs and salaries for HST personnel

Key sensitivity analyses:

The project team conducted univariate and multivariate sensitivity analyses on model parameters to identify the factors with the greatest influence on the clinical and economic value of the HST program. We described thresholds of effectiveness and cost needed to render the HST program cost-effective. We also conducted probabilistic sensitivity analyses, conducting very large numbers of simulations in which we vary multiple parameters through specified distributions simultaneously to determine the proportion of clinical and cost scenarios in which the HST program remains cost-effective.

Potential Limitations Considered at Study Conception

Hiring a motivated HST nurse with inpatient experience would be important. Based on inpatient nurse salaries, adequate money has been budgeted to provide a competitive offer to an early-/mid-career nurse. Alternative strategies include higher salary and flexibility with schedule. If a less-experienced nurse is hired, the amount of time shadowing on the HIV/AIDS unit could be increased.

Some physicians may see patients in hospital units with different control and intervention statuses. The direction of effect of contamination would be difficult to anticipate. For example, having had a patient receive HST medication review, a provider may become more knowledgeable about the meds and more thorough in his/her own review. Alternatively, he or she may shrug off the work, expecting the HST to fill in. The study is adequately powered to withstand some contamination.

However, the degree of any contamination effect may be small, as most providers would only occasionally admit PLWH or persons on HCV Rx (one or two in a 3-month period). Nurses and case managers have highly unit-based roles, so little or no contamination in this setting was expected. Contamination in ascertaining outcomes may happen when patients are transferred within the hospital (e.g., from medicine to surgery). The HST was expected to see patients transferred in and to continue seeing patients who were transferred away.

Action could be taken if interim analysis revealed consent being obtained for <66% of candidate patients. Inadequate time to meet patients can be addressed by adding staff or limiting efforts to patients who appeared to be unengaged in outpatient care, per inpatient chart review.

Results

Overall, our team executed the interventional trial planned in Aim 1, which constituted the bulk of the planned work for the entire project. We have accomplished some analyses of data from the trial, but, based on these results, we have altered several study plans, including stopping all work on Aims 2 and 3 and also pursuing a new direction in designing and studying an automated alert for people living with HCV. These results and the related discussion are described below and are organized along individual project lines. Additional methodology, when relevant, is also described below.

HIV linkage and re-engagement

During the 2-year intervention window (May 201 to May 2019), we observed several anecdotal cases that suggested how a nurse with HIV specialty training might provide needed patient-centered education and case management in order to help PLWH engage in outpatient HIV care. We reported two such cases in "An Inpatient HIV Support Nurse to Promote Engagement in Outpatient HIV Care" in the *Journal of the Association of Nurses in AIDS Care* (full citation below).

Briefly, the first case was of a 43 year-old, undocumented, Spanish-speaking male (CD4 count 84 cells/ cubic millimeter and HIV RNA 73,100 copies/mL) admitted for vision loss due to ocular syphilis. The second case was of a 50 year-old male (CD4 count 48 cells/cubic millimeter and HIV RNA 1.5 million copies/mL) admitted with osteomyelitis from a diabetic foot wound and for whom a routine HIV screening test in the ED resulted positive. Both men had never engaged in outpatient HIV care, and the HIV Support Nurse helped both discuss and plan for barriers, including not understanding that antiretrovirals make HIV survivable and easily manageable, worry about stigma from members of one's church, uncertainty about how HIV is transmitted, lack of trust in healthcare institutions, and lack of healthcare coverage.

Both men successfully linked to outpatient care within a week of hospital discharge and both started on antiretrovirals and achieved undetectable HIV RNA values within several months. We concluded that the HIV Support Nurse offered unique value to the inpatient teams in being able to spend long periods of time counseling about HIV, which was not the primary reason for admission in either case.

In connecting the patient who lacked healthcare coverage to the AIDS Drug Assistance Program, we provided support that would cover antiretrovirals and essential antibiotics from the time of discharge; we made warm hand-offs directly to the two outpatient HIV clinics. We did not think the primary hospital teams could have performed each of these tasks, and we took the anecdotes as evidence supporting the HIV Support Team concept.

As planned in June 2019, the HST finished providing support to all patients admitted as of 5/31/2019, the end of the study admitting window. Through February 2020, we continued collecting data, including reviewing charts for baseline engagement in care, HIV RNA level, and CD4 count data and for 6-month post-discharge data (including clinic visits, repeat hospitalizations, HIV RNA levels, and CD4 counts).

In winter 2020, prior to looking at linkage and engagement outcome results, the study PI and the biostatistician reviewed the original analytic plan and replaced the primary outcome of assessing whether persons who had not been seen in an HIV clinic within 6 months kept at least one outpatient HIV appointment following their discharge. We chose 6-month viral suppression (having at least one HIV RNA <200 copies/mL at

least once within the 6-month period following discharge as the new primary outcome, to be assessed for patients whose baseline HIV RNA levels were ≥ 200 copies/mL.

The rationale for this change was that, since the original planning in 2014, two paradigms in HIV management have changed. First, it has become clear that essentially all PLWH should receive antiretrovirals as soon as reasonably possible after their HIV diagnosis, with a goal of achieving and maintaining perpetual HIV viral suppression. Second, once viral suppression has been achieved and maintained for 6 to 12 months, HIV provider visits can be scheduled yearly or even less frequently as long as laboratory studies confirm ongoing viral suppression, appropriate immune response, and no signs of toxicity. Additionally, from a practical standpoint, hospitalized PLWH often do not remember or may not disclose their most recent HIV provider visit date to a study coordinator. In contrast, HIV viral load results are available broadly across several health systems that utilize the same electronic health record software.

The first meaningful finding from the overall study is that we only captured a total of 992 hospitalizations of PLWH. In 2014, based on best-available data, we had hypothesized a total of 1,400 PLWH hospitalizations on study services in a 2-year period. We believe the decrease was due to at least two factors.

First, hospitalizations among PLWH have been swiftly declining. These declines have been tracked in several studies, including a study co-authored by the PI using a large North American HIV consortium (J Infect Dis 2020), and are also evident in looking at administrative data from the Johns Hopkins Hospital. Improvements in HIV viral suppression and consequent immune recovery are the driving reasons for declining hospitalizations.

The second reason this study's total sample was lower than hypothesized was a failure to capture most hospitalizations on inpatient psychiatry services. Around the start of the intervention, these services changed their status within the electronic medical record, and our electronic alert system therefore did not scan these services when trying to identify hospitalized PLWH. Because a handful of psychiatry service admissions did occur, we did not recognize the general absence until near the midpoint of the 2-year intervention window.

So as not to bias results, we decided at that point to exclude psychiatry admissions from the study. Given that psychiatry services historically constituted about 15% of overall PLWH on our originally intended study population, we estimate this may have amounted to as many as 200 hospitalizations.

Another decrement in the eligible study sample came from a change in hospital practice in which many patients admitted to services throughout the hospital were transferred to the hospital's HIV-specialty service. Because all these patients would receive HIV case management and medication reviews on that service (and would cease to be seen by the study HIV Support Team if randomized to our study intervention), they became ineligible for the study.

The driving reason for the change in hospital practice was the need to maintain the HIV-specialty service census in the setting of decreasing overall admissions of PLWH. In total, 212 patients were transferred in this fashion, yielding 780 total patients in the final study cohort.

As of March 2020, we finished data quality assurance for viral suppression and engagement outcomes for 509 patients (approximately 2/3) of the 780-patient study cohort. The study team was then forced to stop all data quality assurance and data organization so that team members could engage in efforts to care for COVID-19 patients. Interruption due to COVID-19 delayed progress throughout 2020 and some of 2021 as well.

To date, a preliminary analysis of the viral suppression outcome on the 2/3 dataset has yielded several informative findings. The first is that the proportion of patients eligible for the viral suppression outcome (i.e., patients who had uncontrolled HIV RNA at the time of admission) was much lower than expected.

In 2014, we had hypothesized that approximately 46% of hospitalizations would occur to individuals with unsuppressed viral load (based on a hypothesized total N of 1400 hospitalizations, this would mean 644 hospitalizations of PLWH with unsuppressed viral load). Of the 509 patients in our preliminary sample, only 23% (n=118) had unsuppressed HIV RNA at admission, much less than the expected 46%.

Of the 118 hospitalizations of individuals with unsuppressed HIV RNA in the sample, 109 (92%) have fully cleaned and organized data. These 109 hospitalizations were balanced between control (52%) and intervention (48%) and were balanced on demographic characteristics, prior use of antiretrovirals, and baseline CD4 count (median 196 cells/microliter [IQR 56-387] for control and 143 [56-309] for intervention groups), and prior use of antiretrovirals (Table 7).

Table 7. Characteristics of viral suppression outcome preliminary sample				
Characteristic		**Control n = 57 (52%)**	**Intervention n = 52 (48%)**	**P-value**
Median age (IQR)		47 (33-58)	44 (30-57)	0.53
Chart-listed gender	Male/Other	36 (63)	27 (52)	0.24
	Female	21 (37)	25 (48)	
Race/ Ethnicity	Non-Hisp. Black	46 (81)	37 (71)	0.38
	Non-Hisp. White	10 (18)	12 (23)	
	Hisp./Other/Unk	1 (2)	3 (6)	
Admission service type	Surgical	23 (40)	10 (19)	**0.05**
	Internal Med	24 (42)	27 (52)	
	Other Med	10 (18)	15 (29)	
Previously used antiretrovirals		39 (68)	43 (83)	0.12
Baseline CD4, median (IQR)		196 (56-387)	143 (56-309)	0.49

Among these 109 hospitalizations, 60 had available HIV RNA data within 6 months following discharge. Our primary analysis treated no HIV RNA result data available as equivalent to having unsuppressed HIV (HIV RNA >200 copies/mL). In this primary analysis, 24 of 57 (42%) control hospitalizations and 23 of 52 (44%) intervention hospitalizations achieved success in the primary outcome of the patient having at least one HIV RNA measurement below 200 copies/mL within 6 months of discharge. In a secondary analysis restricted to the 60 discharges with HIV RNA follow-up data available, 24 of 29 (83%) of control hospitalizations achieved viral suppression and 23 of 31 (74%) of intervention hospitalizations did.
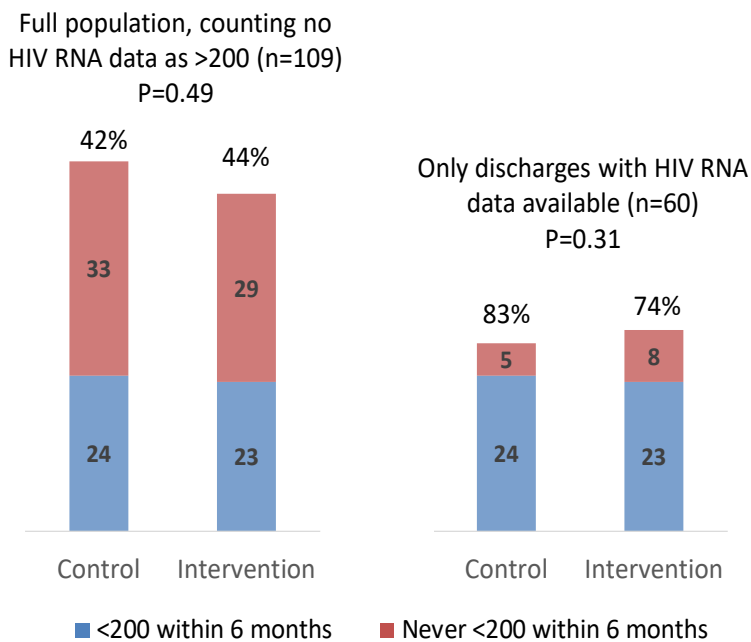
Although these percentages are drawn from only 2/3 of the total study cohort, we can conclude that the HST intervention is unlikely to have had a meaningful effect in encouraging hospitalized patients with unsuppressed HIV RNA to engage in outpatient HIV care after discharge and achieve the critically important clinical outcome of HIV viral suppression. Though disappointing, this result is consistent with two studies published since the design and initiation of the HST project.

Full population, counting no HIV RNA data as >200 (n=109) P=0.49

Only discharges with HIV RNA data available (n=60) P=0.31

■ <200 within 6 months   ■ Never <200 within 6 months

The first, "Hospital Visit as Opportunity for Prevention and Engagement for HIV-infected Drug Users," randomly assigned 750 PLWH with active substance use disorder and baseline detectable HIV RNA to either 1) usual care, 2) intensive care navigation (similar to our intervention), or 3) intensive care navigation plus monetary payments for keeping visits and achieving HIV viral suppression (JAMA 2016). HIV viral suppression at 1 year was no different (34%, 36%, and 39%, respectively) among the three groups.

The second, "Mentor Approach for Promoting Patient Self-Care," randomized 400 inpatients who were not engaged in outpatient care to control educational sessions about safer sex and needle sharing vs. mentoring by volunteer peers with both inpatient visits and post-discharge follow-up phone calls. Thirty-nine percent of control patients compared with 46% of intervention patients (relative risk 1.15, 95% confidence interval 0.94-1.40) (Clin Infect Dis 2016). Taken together, these three studies indicate that intensive, HIV-specific case management starting from the inpatient setting may not be a fruitful area for additional investment by hospitals and HIV providers.

The decrease we noted in the proportion of PLWH with uncontrolled HIV RNA on hospital admission may reflect success from an ongoing national focus to help PLWH initiate and maintain antiretroviral therapy at all times and from the far simpler (typically one-pill-once-a-day) regimens that carry little potential for side effects compared with regimens of just 5 to 10 years ago. Overall, this represents success in one of the most important areas for quality improvement in the care of PWLH. While recognizing this success, it is also important for national efforts to continue focusing on people who remain unengaged in HIV care. These individuals may represent an even harder-to-reach population with all the more need for innovative approaches.

One such approach, and a possible avenue for future work, is promoting rapid (re)start of antiretroviral therapy. In the outpatient setting, starting antiretroviral therapy from the day of (or as soon as possible after) HIV diagnosis has been shown to have a substantial effect in promoting adherence and viral suppression up to a year later (JAMA 2018, AIDS 2018). The same approach could be evaluated in hospitalized patients and extended to include all willing patients not currently taking ART in the outpatient setting, regardless of when they were originally diagnosed and regardless of previous use of ART. This approach counters an historic paradigm of ensuring completed outpatient follow-up visits prior to ART initiation. However, starting ART immediately helps normalize it and reinforces how simple the current regimens are and how unlikely they are to cause side effects.

Existing teams at Hopkins Hospital are, indeed, continuing to focus on the opportunity that hospital encounters provide to help unengaged PLWH become engaged in outpatient care, including by considering rapid ART initiation. The hospital's inpatient Care Coordination Department and the case management team at the large HIV clinic associated with the hospital reached out to this study's PI and are now in the process of restarting the HST's electronic medical record alerts for PLWH admissions. Unit-based case managers throughout the hospital will screen alerted cases for individuals who appear unengaged in outpatient HIV care and will offer resources and a connection to an outreach nurse in the HIV clinic. This nurse may then visit patients at the bedside or communicate by phone to promote engagement in outpatient care and will work with inpatient physician teams to consider rapid ART initiation.

We anticipate completing the data quality assurance and final analysis of the HST effect on post-discharge viral suppression within 2022.

HIV Medication Errors

For the co-primary outcome of antiretroviral-related medication errors, our study team completed data abstraction to identify errors among the 697 hospitalizations (89% of the total 780 hospitalizations) that involved administration of antiretrovirals (note that a number of individuals had uncontrolled HIV on hospital admission but were nonetheless continued on antiretrovirals or started on antiretrovirals during their hospital stay). The review for errors involved several steps, including revising and finalizing the protocol for determining medication errors, which we categorized as incomplete regimen errors, dosing errors, and use of combinations with unsafe drug-drug interaction potential.

The study PI and lead pharmacy investigator, Dr. Fidelia Bernice, then led three post-graduate pharmacy resident trainees in learning the protocol and performing parallel reviews until they achieved over 95% concurrence in identifying errors. During October 2019 to March 2020, the three pharmacy residents abstracted all charts, examining the day of admission, up to 14 hospital days following admission and the discharge medication regimen. This was done without unmasking the assignment to intervention or control.

Incomplete regimen errors can be expected to carry the most important consequences for HIV management, because such errors can result in viral breakthrough and, potentially, development of HIV viral resistance. As such, the abstractors discussed every potential incomplete regimen error in biweekly group meetings together with the study PI. Based on an original sample estimate of 756 hospitalizations involving use of antiretrovirals (the final sample of 697 hospitalizations is roughly similar), we anticipated that 136 hospitalizations would involve a medication error of some type and that 62 hospitalizations would involve incomplete regimen errors.

Instead, based on the adjudication discussions, only three hospitalizations were involved an incomplete regimen error, with only one of these perpetuated in the discharge medication list. In addition, there has been tremendous uptake, since 2015, of one-pill-once-daily regimens, with most of these pills containing three to four co-formulated medicines. Furthermore, there has been a simultaneous reduction in the use of protease inhibitor medications that require separate "booster" pills, which is an obvious major factor underlying the low number of incomplete regimen errors.

The COVID-19 pandemic forced us to halt work to finalize and tabulate the medication error data; the project team has not yet unmasked the assignment to control vs. intervention. Nevertheless, we can interpret two points from the very low number of incomplete regimen errors we observed. First, the number of events precludes comparison between intervention and control. Second, the dramatic shift toward convenient combination regimens can be expected to have dramatically reduced incomplete regimen errors in this country.

HCV Medication Errors

Due to the COVID pandemic, the project team did not have an opportunity to abstract hospitalizations for HCV medication errors. Based on feedback from the HST nurse and pharmacist, we expect there to have been fewer overall errors than originally hypothesized. Two changes in HCV therapy since the time of study design might be expected to cause a decrease in errors. First, there is a decrease in the duration of HCV regimen courses from 3-6 months to 2-3 months; this means that there would be fewer incidental hospitalizations during the course of HCV therapy. Second is consolidation of many HCV regimens into single-tablet combinations, similar to HIV regimens, making incomplete regimen errors unlikely.

Aim 2: Develop a toolkit for non-HIV/HCV expert nurses and clinical pharmacists to learn and perform the HST roles and an implementation strategy for hospitals.

After seeing the evidence that the HST intervention was not effective at improving post-discharge viral suppression or at preventing important medication errors, the project team discontinued work on a toolkit for an HST program. However, materials were started on all aspects, which would allow for them to be resumed if the picture changes.

Aim 3: Use the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model to project the HIV-related clinical outcomes, costs, and cost-effectiveness of the HST intervention.

Similarly, after seeing that the HST intervention was not effective at improving post-discharge viral suppression or major medication errors, the project team realized there was no utility in continuing to work on the development of a model for cost-effectiveness analysis. Drs. Berry and Ciaranello searched for another program for hospital-based engagement in care. A program at the Massachusetts General Hospital was considered, but that program ultimately also did not show efficacy. Thus, the project team decided against continuing work on this aim.

Electronic Medical Record HIV Alert System

During 2020 and 2021, the project team conducted an evaluation of the electronic alert system used to identify PLWH at the time of hospital admission. Two research associates abstracted data from our electronic medical record (EMR) to assess the alert system's sensitivity. In 2021, we extracted an additional dataset from the hospital EMR to assess the positive predictive value of each component of the alert A post-doctoral fellow has organized, quality assured, and analyzed the data and has submitted a manuscript for publication.

In brief, the EMR alert was designed to trigger for at least one of the following criteria: (1) an HIV ICD-10 code in a problem list, (2) HIV antiretroviral medication(s) on medication lists, (3) an HIV-1 RNA level assay ordered,or (4) a positive HIV antibody result. We used manual chart reviews and an EMR database search to determine the sensitivity and the positive predictive value (PPV) of the overall alert and of its individual criteria.

Over the planned 24-month intervention period, the alert functioned as intended, notifying both our intervention team and our data abstraction team about admissions of PLWH. Manual review of an approximately 3% sample of annual hospitalizations to adult services (1634 hospitalizations) identified 18 hospitalizations of PLWH, all of which were captured by the alert (sensitivity 100%, 95% CI: 82%-100%). Over the 24 months, the alert triggered for 1191 total hospitalizations. Of these, 992 were hospitalizations of PLWH (PPV=83.3%; 95% CI: 81.2, 85.4).Using fewer criteria (e.g., using only ICD-10 codes) identified fewer PLWH but increased the PPV.

The project team concluded that our EMR alert was effective in accurately identifying hospitalized PLWH for the HST quality improvement intervention. The main limitation of our analysis was our sample size for assessing the sensitivity of the alert; it required a manual chart review of over 1600 cases to identify 18 PLWH. In this regard, the EMR alert's capture of all 18 was at least reassuring.

Because the EMR data elements used for the alert will be similar in EMR software used by other hospitals, the project team expects the alert might be easily exportable for quality interventions among PLWH at other centers. Last, we think that similar alerts might be used for quality and safety interventions (e.g., activating support teams, alerting medical specialists, and/or prompting clinical care pathways) in other chronic diseases. Possibilities include HCV, diabetes, and rheumatologic disorders.

Our study's HIV alert is novel. The project team hypothesize that healthcare providers could design similar alerts to identify hospitalized persons who are experiencing other concurrent diseases, such as chronic viral hepatitis, diabetes, or chronic inflammatory diseases. Alerts could be used to improve care of these diseases by activating support teams, alerting medical specialists, and/or prompting electronic clinical care pathways.

Hospital Alert for Targeting Chronic HCV (HATCH)

In summer 2020, with the preliminary results of the EMR HIV alert analysis apparent, the project team undertook a new project to design and evaluate an alert to identify hospitalized patients living with chronic hepatitis C who have not yet achieved a sustained virologic response (a cure) following treatment with HCV antivirals. Although there has been substantial progress on this project to date, the work is not done. The rationale, project design, and progress are described below.

The population of interest for this alert, persons with uncured HCV, is many times larger than the population from Aim 1, persons hospitalized (by chance) during the several-week window of taking a course of HCV medicines. Similar to HIV, helping untreated persons with HCV get treated is a public health priority. As described earlier, more Americans are living with HCV than with HIV, and complications of HCV now claim more lives annually.

The majority of Americans living with HCV are asymptomatic from it and have not linked to HCV care, and hospitalizations (generally for non-liver-related reasons) may be an ideal opportunity for linkage efforts. Analogous to the HIV alert, we aim to demonstrate the feasibility and accuracy of an EMR-based alert to identify persons living with uncured HCV. We are not undertaking outreach and linkage efforts on the alerted patients at this time, but HCV providers are advising the project and may consider a future intervention that uses the alert messages.

The alert has been designed to use the following criteria to screen patients hospitalized for hepatitis C:
1. A previously positive hepatitis C Ab test
2. A previously positive hepatitis C quantitative RNA PCR
3. Any hepatitis C diagnosis codes in their problem lists or orders

The following two criteria are then used to determine if identified patients have already been treated:

1. A negative hepatitis C quantitative RNA PCR after an initial positive
2. Any history of oral direct acting antiviral hepatitis C medications

Based on experience with the HIV alert, the project team planned an initial design and refinement period with periodic manual checks for both sensitivity and positive predictive value of the alert criteria. We estimated that this refinement period would include review of at least 100 initial alerts among hospitalized adults, though we allowed that it may include more reviews as needed to eliminate obvious flaws.

The study plan following the refinement period is as follows:

Population: The population for determining positive predictive value will be adults hospitalized at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center on all inpatient services, including psychiatry services, for a 6-month period or for longer than 6 months (until at least 1000 alerted hospitalizations accrue).

Based on historic admission volumes and HCV prevalence in Baltimore, the team expects 1000 to 1500 alerted hospitalizations within 6 months in total among both hospitals. The population for determining sensitivity will consist of an equal number of adult hospitalizations randomly selected (without regard to whether the HCV alert fired) from the same adult admitting services over the same time period.

Primary Outcome Variable: Binary variable indicating presence of uncured HCV or not

Secondary Outcome Variables: Which component(s) of the alert fired (for PPV population); whether the HCV alert fired (for the sensitivity population)

Covariates: Demographics, hospital admission date, hospital (Hopkins Hospital or Bayview Hospital); ascertainment of outcomes and covariates will be through manual chart review

Sample Size: Assuming a PPV between 80% and 90% with a goal of 2% precision of our estimate with 95% confidence, the estimated needed sample size is between 850 and 1500.

Although there was progress in the study, there were unanticipated delays The Institutional Review Board approval was granted in March 2021, 4 months after initial submission, with a change in status from Quality Improvement/non-Human Subjects Research to Secondary Research.

The project team believes that the long duration of IRB review was from a backlog in IRB reviews related to COVID; there were no human subject-related concerns raised. Second, the alert build has required more iterations in the refinement period than anticipated.

To date, the alert has been through six iterations. The project team has reviewed about 160 charts in the process of looking for failures of the alert criteria to trigger as intended. One of the major challenges has been accurately capturing persons who have a positive antibody result but have no HCV RNA values available.

The project team is currently waiting to confirm a version with complete capture of ICD codes from multiple problem lists. Then, we anticipate moving to the data collection phase of approximately 6 months duration. The project team plans to complete the data collection and analysis during 2022.

Results Summary

Overall, our results for the HIV/HCV support team work have led us to reject hypotheses about the impact of a nurse and pharmacist-led team for decreasing HIV-related medication errors and improving engagement in outpatient HIV care. Although this was not the original projected outcome, it does provide information for hospitals that efforts to improve HIV care should be focused on other areas.

The project demonstrated major changes in the field of HIV medicine, including a dramatic shift toward single-tablet regimens with extremely low rates of side effects and drug interactions and a progressive and highly desirable shift toward more PLWH coming into care and achieving viral suppression on these regimens.

Finally, the EMR alert that facilitated our interventional study is novel and was successful. The results of the analysis of its accuracy, as well as a description of lessons learned in the process of creating it, are an important finding; the project team is in the process of submitting a manuscript on this topic. Furthermore, the EMR alert led to an ongoing project to demonstrate that a similar alert might be used to identify persons living with untreated HCV.

List of Publications and Products

Holmes E, Thompson D, Michell D, Smith JM, Zoltick MI, Gebo KA, Moore RD, Eldred L, Ciaranello A, and Berry SA. An Inpatient HIV Support Nurse to Promote Engagement in Outpatient HIV Care. J Assoc Nurses AIDS Care. 2019 Mar-Apr;30(2):245-248. doi: 10.1097/JNC.0000000000000017. (PMC6427905)

El-Nahal W, Grader Beck T, Gebo KA, Holmes E, Herne K, Moore RD, Thompson D, and Berry SA. Designing an Electronic Medical Record Alert to Identify Hospitalized Patients with HIV: Successes and Challenges. (under submission)

Inventions: None

References: Contact author(s) and/or author institutions for citation details.