A Call to Action: The Role of Antiretroviral Stewardship in Inpatient Practice, a Joint Policy Paper of the Infectious Diseases Society of America, HIV Medicine Association, and American Academy of HIV Medicine

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Persons living with human immunodeficiency virus (HIV) and others receiving antiretrovirals are at risk for medication errors during hospitalization and at transitions of care. These errors may result in adverse effects or viral resistance, limiting future treatment options. A range of interventions is described in the literature to decrease the occurrence or duration of medication errors, including review of electronic health records, clinical checklists at care transitions, and daily review of medication lists. To reduce the risk of medication-related errors, antiretroviral stewardship programs (ARVSPs) are needed to enhance patient safety. This call to action, endorsed by the Infectious Diseases Society of America, the HIV Medicine Association, and the American Academy of HIV Medicine, is modeled upon the success of antimicrobial stewardship programs now mandated by the Joint Commission. Herein, we propose definitions of ARVSPs, suggest resources for ARVSP leadership, and provide a summary of published, successful strategies for ARVSP that healthcare facilities may use to develop locally appropriate programs.

Keywords. HIV; antiretroviral; stewardship.

Modern combination antiretroviral (ARV) therapy has introduced an era of unprecedented freedom from life-threatening opportunistic infections and cancers resulting in increased longevity. As persons living with human immunodeficiency virus (PLWH) and others receiving ARVs benefit from these therapeutic advances, signals of an increased incidence of chronic, noncommunicable health conditions (cardiovascular disease, chronic kidney disease, diabetes, and malignancy) have become apparent. Even though hospitalization rates among PLWH have decreased due to effective ARV therapy, the potential for ARV-related errors persist during admission to and discharge from the hospital [1]. Vigilant pharmacologic management of ARVs in the inpatient setting has now evolved to include not only evidence-based selection of appropriate ARVs, but also management of concurrent infectious and noninfectious complications and comorbidities, which require careful selection of concomitant drug therapy.

Patients receiving ARVs remain at significant risk of medication errors related to the ARVs themselves or other concomitant medications during hospitalization [2–5]. The frequency of inpatient ARV errors varies greatly based on study design and institution, but rates have been reported as high as 86% [3]. The most common errors, based on a variety of studies, include drug omissions in a patient’s ARV regimen, incorrect dosing/scheduling of ARVs, and drug interactions [2–5]. ARV-related errors can lead to new or increased adverse effects, treatment failure, or drug resistance, especially if not corrected promptly. Most data on ARV-related errors have been evaluated in retrospective studies in which errors may or may not have been rectified during hospital admission. The ability of an institution to correct such errors may be dependent on resources (such as dedicated clinicians to systematically review ARV orders and/or the presence of targeted interventions toward ARV-related error reduction). One study conducted at an urban academic medical center and based on a clinical pharmacist’s review of patients receiving ARVs reported correction of most ARV-related errors within 48 hours; however, another urban academic medical center with a part-time dedicated clinical pharmacist reviewing patient records reported only a 24% error correction rate prior to discharge [2, 5].
The challenges of ARV-related medication errors are predicted to increase. Almost half of American PLWH are ≥50 years of age and have a higher prevalence of comorbidities compared with human immunodeficiency virus (HIV)–negative persons of identical age [6, 7]. The additional indications of ARVs for hepatitis B treatment and HIV preexposure and postexposure prophylaxis have only expanded the therapeutic use of these medications. The increasing prevalence of these associated indications and consequent prescription of ARVs increase the potential for drug interactions and therapy-related errors [8]. Therapeutic decisions to continue, adjust, or withhold treatments prescribed in the outpatient setting (in addition to transitioning patients to outpatient care) are of critical importance to improve both individual patient safety as well as public health considerations.

As a quality assurance standard to improve appropriate utilization of antimicrobials, optimize antibiotic treatments, reduce microbial resistance, and avoid adverse outcomes associated with antibiotic use, antimicrobial stewardship programs (ASPs) have been well integrated into the great majority of inpatient settings over the past 10–20 years [9]. The Centers for Disease Control and Prevention recognizes and recommends utilizing these programs to address patient safety and public health concerns [10]. In comparison, stewardship activities for ARVs described here have only been recently implemented and share similar goals of addressing patient safety and error reduction for hospitalized patients in transitions of care and throughout hospitalization.

ANTIRETROVIRAL STEWARDSHIP

The combined statement from the Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society defines antimicrobial stewardship as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen, including dosing, duration of therapy, and route of administration” [11]. Furthermore, standard MM.09.01.01 (effective 1 January 2017) from the Joint Commission mandates that a “[critical access] hospital [have] an antimicrobial stewardship program based on current scientific literature” [12]. Nevertheless, ARV-related errors continue to persist, demonstrating the need for an expanded definition of hospital-based ASPs that include the management and monitoring of ARVs.

We build upon the existing definition of antimicrobial stewardship and encourage the expansion of this important area of practice to include ARV stewardship, defined as “coordinated interventions designed to improve continuity of care for patients receiving ARVs through the utilization of evidence-based ARV practices including medication reconciliation, dosing, mitigation of drug interactions, and prevention of viral resistance.”

COMPONENTS OF AN ANTIRETROVIRAL STEWARDSHIP PROGRAM

Antiretroviral stewardship programs (ARVSPs) should seek to provide comprehensive and cost-effective care for the purpose of achieving outcomes that improve the quality of life of any person receiving ARVs. An ARVSP should provide guidance and/or a forum for collaboration between pharmacists, physicians, and other healthcare professionals to optimize drug therapy outcomes with a focus on ARV management. Such programs may include, but are not limited to, tracking and reporting utilization of ARVs, completing prompt and accurate medication reconciliation, assisting primary care services with transitions of care, assessing engagement in care, linkage to care between inpatient and outpatient disease-state management, and educating healthcare providers and other healthcare learners. Furthermore, institution-specific needs may include streamlined computerized provider order entry (CPOE) for ARV combination products and individualized strategies for medication formulary management to meet the needs of local patients. These responsibilities may include, but are not limited to, the addition of ARVs to a medication formulary of an institution, collaborations with medication suppliers/outpatient pharmacies to quickly supply the hospital with required ARVs, or the creation of policies that allow patients to use previously prescribed ARVs from home while hospitalized.

LEADERSHIP AND OVERSIGHT OF ARVSPS

ARVSP oversight should be supervised by healthcare providers who are proficient and experienced in the management of ARVs for their clinically relevant indications. In hospital settings, such providers may be defined by their clinical expertise and experience across several specialties, including infectious diseases (ID), internal medicine, family medicine, qualified advanced practice providers, and pharmacists. To help define ARV expertise, minimum criteria defined by the HIV Medicine Association (HIVMA) guidelines for HIV specialization include longitudinal clinical care of at least 25 PLWH over at least 36 months, HIV-focused continuing education, and board certification in one or more medical specialties as defined by the American Board of Medical Specialties or the American Osteopathic Association; HIVMA recognizes a minimum of 5 years’ experience in lieu of board certification [13]. The American Academy of HIV Medicine (AAHIVM) requires clinical experience in caring for at least 20 PLWH over at least 36 months, HIV-focused continuing education, and successful completion of a credentialing examination for physicians, nurse practitioners, physician assistants, pharmacists, and nonclinical experts [14]. While the HIVMA and AAHIVM criteria for defining HIV specialization are not the only guidelines for defining ARV expertise, they may be beneficial in identifying healthcare providers who are best suited to guide inpatient
ARV stewardship for hospitalized patients. For institutions or providers looking to strengthen ARV expertise, additional resources can be found in the following sections.

**APPROACHES AND STRATEGIES FOR ARVSPS**

There have been numerous strategies for ARVSPs described in the medical literature, all intended to decrease medication errors and clinically significant drug interactions [4, 15–27]. Among various methods of implementing ARVSPs, the different approaches can be separated into 3 main categories: (1) checklists to ensure safe prescribing practices; (2) CPOE sets; and (3) prospective review strategies by physician-pharmacist collaborations for anticipated needs of PLWH during hospitalization. To offer guidance to institutions considering ARVSP interventions appropriate for their individual setting, Table 1 summarizes published ARVSP strategies.

Clinical checklists upon admission and at the time of order entry have been used successfully in outpatient and inpatient settings to reduce errors and improve outcomes [20, 26]. Studies evaluating these checklists have demonstrated reductions in medication errors and increases in prescription of optimized ARV regimens based on viral resistance, safety, regimen simplification, avoidance of drug interactions, and improved rate of virologic response [20]. The use of the electronic health record may also be leveraged to increase patient safety through approaches such as specially created CPOE order sets with guided ARV ordering instructions, display of best-practice advisory alerts, notification of contraindicated drug combinations, inclusion of administration recommendations (eg, with food or with required pharmacokinetic boosters), and provision of reference links to electronic databases [18–21, 24]. These CPOE interventions have demonstrated reductions in ARV-related errors by >40%, particularly with protease inhibitor–based regimens for HIV treatment [18, 21, 22]. Regardless of the tools used, successful execution of these checklists or CPOE stewardship interventions are dependent on education and feedback for clinicians throughout implementation of interventions as well as ongoing clinical support to keep them updated [18–22].

Prospective review strategies also decrease ARV-related errors [4, 15–17, 19–27]. This approach is often facilitated by clinicians and pharmacists specializing in HIV/ID and based on either electronic health record–generated patient lists or the use of nonformulary or restricted statuses of ARVs. A single review of ARVs at the time of admission has been shown to decrease the rate of errors; it may not prevent medication errors throughout hospitalization when additional medications are added or when the clinical status of the patient changes (eg, fluctuations in renal function, need for intubation, or inability to swallow). In contrast, daily medical records review of all hospitalized patients on ARVs has also resulted in significant reductions in medication errors; utilizing a clinical pharmacist specialist or experienced HIV/ID provider to monitor patients throughout hospital admission has the potential to identify and mitigate up to 95% of drug interactions [16, 17, 19, 22]. A study evaluating the impact of pharmacist interventions for ARV-related errors resulted in 90% acceptance rate of pharmacists’ recommendations, with an average time of 18.5 minutes of pharmacist’s time per patient requiring an intervention [25].

**RECOMMENDATIONS AND OPPORTUNITIES**

Expanded stewardship programs that include an emphasis on ARVs can prevent virologic failure, viral resistance, deleterious drug interactions, and adverse drug events. Unlike antibiotics, ARVs are often prescribed in the inpatient setting in continuation of an outpatient regimen, highlighting the importance of selected attention to these medications that are associated with a high risk of error during transitions of care from hospital admission to discharge. This requires accurate medication reconciliation; an in-depth knowledge of ARV pharmacology; and, if changes to the ARV regimen are required, a thorough review of social history and past medical history. To achieve optimal outcomes, an interdisciplinary team dedicated to ARV management is imperative. Due to the potential for permanent viral resistance to ARVs and the high cost of ARV medications, institutions can prioritize ARV stewardship by developing policies regarding ARV acquisition, management, and review to minimize risk to both the patient and the institution. As such, the IDSA, HIVMA, and AAHIVM endorse the following statements:

1. ARV-directed stewardship improves the safety of patients receiving ARVs and can be incorporated into existing stewardship initiatives using strategies appropriate for the institution, for the number of patients receiving ARVs hospitalized per year, and for local expertise.
   a. Institutions can implement or augment their existing structures to include an interdisciplinary team that includes an HIV/ID-trained pharmacist and/or provider to manage, maintain, and monitor stewardship initiatives.
   b. Institutions can align with local, state, and national organizations, departments of health, or other agencies tasked with monitoring public health to maintain updated treatment and prevention protocols.
2. Accrediting, regulatory, and quality assurance organizations can broaden the scope of existing stewardship definitions to include ARVs and the care of patients receiving ARVs.
3. Institutions can create individualized policies to address ARV formulary management to ensure the continuity of ARV therapy during hospital admission and seamless transitions to outpatient care upon discharge.
| Citation      | Institution Type | Tools                                | Personnel                                      | Description of the Intervention                                                                                                                                                                                                                   |
|---------------|------------------|--------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Batra et al, 2015 [22] | 627-bed academic institution | Prospective chart review | HIV-specialized pharmacist | EHR-generated list of PLWH during weekdays<br>Weekend admissions were reviewed on the next business day                                                                                                 |
| Bias et al, 2014 [15] | 416-bed community teaching hospital | Prospective chart review CPOE intervention | Pharmacy resident supervised by HIV-specialized pharmacist | CPOE prompts prescriber to contact ARVSP (available 24/7)<br>Approval of ARV is required, unless prescribed by ID specialist<br>Patient interviews conducted to assess appropriateness of therapy                                                                 |
| Billedo et al, 2016 [17] | 464-bed community teaching hospital | Prospective chart review CPOE intervention | Pharmacy resident supervised by HIV-specialized pharmacist | ARVSP expansion from Bias et al [15], with daily review of PLWH throughout hospitalization                                                                                                     |
| Carcelero et al, 2011 [23] | 750-bed academic institution | Prospective chart review | Pharmacy resident supervised by ID-specialized pharmacist | List generated twice weekly of patients prescribed ARVs                                                                                                                                                                                      |
| Daniels et al, 2012 [24] | 803-bed academic institution | Prospective chart review CPOE intervention Directed ARV education | ID pharmacy resident ID specialized pharmacist ID consult service | CPOE alerts for incorrect doses and DDIs; common ARV dose defaults<br>Addition of all combination ARV products to the formulary listed by proprietary names<br>Primary service notified ID consult service to review ARVs of newly admitted patients<br>Clinical pharmacists review new ARV initiations<br>Daily review conducted through hospitalization<br>Distribution of pocket-sized references with doses, dosage forms, and frequencies to physicians and pharmacists                                                                 |
| DePuy et al, 2019 [16] | 722-bed academic institution | Prospective records review CPOE intervention Directed ARV education | ID specialized pharmacist ID consult service | EHR-generated list of patients receiving ARVs during weekdays (weekend admissions reviewed on the next business day)<br>CPOE alerts for incorrect doses and DDIs; common ARV dose defaults<br>Daily review conducted through hospitalization<br>Distribution of pocket-sized references with doses, dosage forms, and frequencies to physicians and pharmacists<br>Creation of HIV-focused reference materials (common doses, DDIs, dose defaults, and contraindications) |
| Eginger et al, 2013 [25] | 695-bed academic institution | Prospective records review | Pharmacy resident | EHR-generated list of patients receiving ARVs or opportunistic infection medications at least 3 times per week<br>Interventions made within 72 hours of admission (if possible)                                                                 |
| Guo et al, 2015 [18] | 1400-bed academic institution | Prospective records review CPOE intervention Directed ARV education | HIV-specialized nurse practitioner | ARV orders reviewed by HIV-specialized nurse practitioners<br>Customized CPOE developed by HIV specialists and antimicrobial stewardship providers to guide appropriate ARV prescribing (dosing, contraindications, incomplete regimens)<br>Monthly trainings for staff, physician assistants, and pharmacists<br>Creation of HIV-focused reference materials (common doses, DDIs, dose adjustments, and contraindications) |
| Heelion et al, 2007 [26] | 651-bed academic institution | Prospective records review Clinical checklist | Clinical pharmacist | Generation of list with ARV-receiving patients on weekdays (weekend admissions were reviewed on the next business day)<br>Implementation of a CPOE-based checklist with focus on accuracy of ARV regimen, dosing, DDIs, and opportunistic infection prophylaxis |
| Lauzevis et al, 2013 [27] | 489-bed community hospital | Prospective records review | Pharmacist HIV-specialized physician | Pharmacist communication with the physician on weekdays based on computerized order of ARVs (weekends orders were communicated on the next business day)<br>Physician determination of the appropriateness of therapy based on outpatient records (when available) |
| Liedtke et al, 2016 [4] | 680-bed academic institution | Prospective records review | HIV-specialized pharmacist | EHR-generated list of patients receiving ARVs during weekdays (weekend admissions reviewed on the next business day) |
| Sanders et al, 2014 [19] | 1398-bed academic institution | Prospective records review CPOE intervention Directed ARV education | ID pharmacy resident ID-specialized pharmacists ID physicians | CPOE removal of dose/frequency options inappropriate for individual ARVs<br>Records review by physicians and pharmacists at transitions of care; daily review of hospitalized patients receiving ARVs<br>Creation of education for ID and pharmacy departments including a mandatory online module for pharmacists |
In summary, various methods of ARV stewardship have been shown to identify, correct, and prevent ARV-associated medication errors. ARVSPs can enhance clinical outcomes, prevent viral resistance to ARVs, and improve overall inpatient management. Similar to the implementation of ASPs, ARVSPs will require advocacy, assessment of best practices, and a multidisciplinary, institutional-based approach to achieve improvements in patient care.

**ADDITIONAL RESOURCES**

- US Department of Health and Human Services: AIDSinfo (www.aidsinfo.nih.gov)
- AIDS Education and Training Centers (www.aidsetc.org)
- University of Liverpool HIV Drug Interactions (www.hiv-druginteractions.org)
- HIV and Aging (www.hiv-age.org)
- American Academy of HIV Medicine (www.aahivm.org)
- HIV Medicine Association (www.hivma.org)

**Notes**

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**References**

1. Paul S, Gilbert HM, Lande I, et al. Impact of antiretroviral therapy on decreasing hospitalization rates of HIV-infected patients in 2001. AIDS Res Hum Retroviruses 2002; 18:501–6.
2. Chompras TD, Kim H, Badowski M. Evaluation of the occurrence and type of antiretroviral and opportunistic infection medication errors within the inpatient setting. Pharm Pract (Granada) 2015; 13:512.
20. Shea KM, Hobbs AL, Shumake JD, Temple DJ, Padilla-Tolentino E, Mondy KE. Impact of an antiretroviral stewardship strategy on medication error rates. Am J Health Syst Pharm 2018; 75:876–85.

21. Zucker J, Mittal J, Jen SP, Cheng L, Cennimo D. Impact of stewardship interventions on antiretroviral medication errors in an urban medical center: a 3-year, multiphase study. Pharmacotherapy 2016; 36:245–51.

22. Batra R, Wolbach-Lowes J, Swindells S, et al. Impact of an electronic medical record on the incidence of antiretroviral prescription errors and HIV pharmacist reconciliation on error correction among hospitalized HIV-infected patients. Antivir Ther 2015; 20:555–9.

23. Carcelero E, Tuset M, Martin M, et al. Evaluation of antiretroviral-related errors and interventions by the clinical pharmacist in hospitalized HIV-infected patients. HIV Med 2011; 12:494–9.

24. Daniels LM, Raasch RH, Corbett AH. Implementation of targeted interventions to decrease antiretroviral related errors in hospitalized patients. Am J Health Syst Pharm 2012; 69:422–30.

25. Eginger KH, Yazborough LL, Inge LD, Basile SA, Floresca D, Aaronson PM. Medication errors in HIV-infected hospitalized patients: a pharmacist’s impact. Ann Pharmacother 2013; 47:953–60.

26. Heelon M, Skiest D, Tereso G, et al. Effect of a clinical pharmacist’s interventions on duration of antiretroviral-related errors in hospitalized patients. Am J Health Syst Pharm 2007; 64:2064–8.

27. Lauzevis S, Chaix F, Lazzerini C. Evaluation of a strategy aimed at reducing errors in antiretroviral prescriptions for hospitalized HIV-infected patients. Med Mal Infect 2013; 43:391–7.