DESCRIPTION OF FACTORS ASSOCIATED WITH MEDICATION ERRORS IN AN HIV AMBULATORY CARE SETTING: THE DEFEAT STUDY

Niamh Higgins

Department of Epidemiology, Biostatistics and Occupational Health
McGill University, Montreal

August 2011

A thesis submitted to McGill University, Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the Master of Science degree

ABSTRACT

Objective: The purpose of the DEFEAT Study was to better characterize medication errors in patients infected with HIV and identify the risk factors associated with these errors.

Method: The DEFEAT Study was cross-sectional by design. Pharmacists conducted patient interviews in order to obtain best possible medication histories. Two pharmacists independently evaluated the medication profiles of each patient for therapeutic appropriateness. Medication errors were classified by severity using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index for Categorizing Medication Errors. Risk factors for the number of errors per patient were identified using Poisson regression. Risk factors for error severity were identified using a proportional odds model.

Results: Pharmacists interviewed 151 patients and identified a total of 1,699 errors; 224 errors reached patients, of which 133 required intervention. Possible risk factors included certain medication classes, such as chemotherapy, erectile dysfunction drugs, inhalers and anti-infectives; the number of concomitant medications; the number of over-the-counter products; years since HIV diagnosis; history of cardiovascular disease; and collecting prescriptions from more than one pharmacy.

Conclusions: In this sample of ambulatory patients with HIV, pharmacists identified a high number of medication errors that reached patients. Further research will focus on developing systems-based approaches to improve medication safety practices.

RÉSUMÉ

Objectif: L'objectif de l'étude DEFEAT est de mieux définir les erreurs de médication chez les patients infectés par le VIH, et d'identifier les facteurs de risque associés à ces erreurs.

Méthode: Des pharmaciens ont fait des entrevues avec les patients pour obtenir la meilleure histoire médicamenteuse possible. Deux pharmaciens ont indépendamment évalué les profils médicamenteux de chaque patient pour vérifier leur conformité aux indications thérapeutiques. Les erreurs médicamenteuses ont été classées par ordre de sévérité en utilisant l'index de catégorisation des erreurs médicamenteuses du « Conseil National pour le signalement et la prévention des erreurs médicamenteuses » (Le NCC MERP). Les facteurs de risque pour le nombre d'erreurs par patient ont été identifiés en utilisant la régression Poisson. Les facteurs de risque pour la sévérité des erreurs ont été identifiés en utilisant un modèle chance proportionné.

Résultats: Les pharmaciens ont interrogé 151 patients, et identifié un total de 1699 erreurs; 224 erreurs s'étendaient aux patients, dont 133 ont nécessité une intervention. Les facteurs de risque possibles incluaient certaines classes de médicaments, tels ceux utilisés en chimiothérapie, pour les dysfonctions érectiles, les inhalateurs et anti-infectieux, le nombre de médicaments concomitants, le nombre de produit vente libre, le nombre d'années écoulées depuis le diagnostic de VIH, histoire de maladie cardio-vasculaire, et le fait d'avoir des prescriptions dans plus d'une pharmacie.

Conclusions: Dans cet échantillon de patients infectés par le VIH, les pharmaciens ont identifié un nombre élevé d'erreurs médicamenteuses atteignant les patients. Des recherches plus poussées se concentreront sur le développement d'approches basées par système pour améliorer les pratiques de médications sécuritaires.

STATEMENT OF SUPPORT

The Canadian Medical Protective Association (CMPA) funded the DEFEAT Study through a Collaborative Research Grant. The CIHR Canadian Observational Cohort Collaboration (CANOC) supported me through a scholarship award while I completed this research.

ACKNOWLEDGEMENTS

I would like to gratefully recognize and give my sincerest thanks to the following people who contributed their time, advice, support and encouragement towards the DEFEAT project and my Master's thesis:

Dr. Marina Klein, my primary supervisor and my colleague, for inspiring me to pursue my Master's in epidemiology, for her willingness to mentor, support and encourage me, and for believing in my potential as a researcher.

Dr. Erica Moodie, my co-supervisor, for expressing an interest in my research, for her exceptional availability, constant motivation, and for sharing her wisdom and expertise regarding the statistical methods.

Dr. Pierre Ernst, supervisor of the intensive program for clinicians and member of my thesis committee, for his guidance throughout the program, his advice regarding the project results and for motivating me to stay on track.

Josianne Gauthier, my pharmacy colleague, for her unceasing dedication to the project, and specifically for conducting many of the study visits and for spending long hours outside of work to meticulously evaluate each patient's chart for medication errors.

Leala Wong, our extraordinary research coordinator, for her amazing recruitment skills, organizational abilities and her superb attention to detail regarding data entry and management.

Sahar Saeed, our clinic research project manager, for her continuous encouragement, for being a great listener, for her support and guidance throughout the course of this research project, and particularly for her advice and assistance with managing the CMPA grant.

Shirley Brugerie, our clinic research ethics coordinator, for organizing the lengthy ethics process and managing all of the issues pertaining to ethics throughout the course of the project.

Dr. Martin Potter, my colleague, for taking an interest in the project idea, for assisting with the protocol development and the grant application, for being a sounding board and for encouraging me throughout the Master's program.

Dr. Richard Lalonde, our former clinic medical director, for supporting the project research activities and encouraging me as a new researcher.

Nancy Sheehan, my pharmacy colleague, for graciously assisting with the final study visits and sharing her expertise as an HIV pharmacist.

Marie Courchesne, my pharmacy supervisor, for her willingness to accommodate the project research activities in spite of the pharmacy-staffing deficit.

Benoit Lemire, my pharmacy colleague, for devoting his time to share his expertise regarding the error analysis.

Our wonderful clerical staff, for facilitating the screening and study visits.

My incredible family and friends, for their positive energy and encouragement.

And finally, the study participants, for their willingness to enroll in the study and take time out of their personal schedules to attend the study visits and for making me realize the aspect of my job that I enjoy most.

DEDICATION

I would like to dedicate this work to my amazing husband and biggest supporter, Eric, for constantly motivating me, for helping me to recognize my qualities and for always making my day brighter.

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LIST OF ABBREVIATIONS

ADE	Adverse drug event
ART	Antiretroviral therapy
ARV	Antiretroviral
BIC	Bayesian Information Criterion
BMA	Bayesian Model Averaging
CAM	Complementary and alternative medicine
CDS	Clinical decision support
CI	Confidence interval
CPOE	Computerized physician order entry
CSDI	Clinically significant drug-drug interactions
DEFEAT	Description of Factors associated with Medication Errors in an HIV Ambulatory Care Setting
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IDU	Injection drug use
IDS	Immunodeficiency Service
IQR	Inter-quartile range
ISMP	Institute for Safe Medication Practices
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OR	Odds ratio
PADE	Potential adverse drug event
PI	Protease inhibitor
PLHA	People living with HIV/AIDS

POM	Proportional odds model
SMAQ	Simplified Medication Adherence Questionnaire

INTRODUCTION

Medication errors are of major public health importance. Adverse drug events (ADEs), defined as any injury due to medications[1], result in more than 100,000 deaths annually in the United States alone[2,3]. Best estimates suggest that 28% to 56% of ADEs could be avoided[1,2,4,5]. Preventable ADEs prolong hospital stay by 4.6 days and cost one 700-bed teaching hospital approximately $2.8 million annually[5]. Although a considerable number of medication errors may occur in the ambulatory care setting, there is a limited amount of research in this domain[6,7].

People living with HIV/AIDS (PLHA) are a noteworthy population in which to study medication errors. Antiretroviral (ARV) regimens are often complicated and dosing errors can result in virological failure or drug toxicity[8]. Moreover, PLHA are now living long enough to experience HIV as a chronic disease state with challenging comorbid illnesses and complications that require pharmacotherapy. Hence, there is a great potential for clinically significant drug-drug interactions (CSDI) that place patients at risk for ADEs or for drug-resistance. A growing body of literature describes ARV medication errors that resulted in true or potential patient harm[7-30]. Previous studies have focussed largely on ARV medication errors among hospitalized patients[8,9,13,15,16,23-25,27,31]. There is a modest amount of literature on medication errors in the HIV ambulatory care setting[12,17-19,30,32-34]. Further research in this area is warranted given the rapid development of new ARV agents, new drug coformulations, and an aging HIV population with comorbidities and consequent polypharmacy.

The Immunodeficiency Service (IDS) at the Montreal Chest Institute is one of the largest university-affiliated, HIV ambulatory care clinics in Canada, serving over 1,600 patients per year. The clinic receives more than 19,000 patient visits and 550 additional walk-in visits per year. Furthermore, staff physicians write collectively as many as 3,000 prescriptions per year. At the IDS there is a need to quantify the frequency of medication errors, pinpoint the stage at which these errors occur and investigate the clinical factors that place patients at a higher risk of experiencing a medication error. We conducted the

DEscription of Factors Associated with Medication Errors in an HIV Ambulatory Care SeTting Study (DEFEAT Study) to better characterize medication errors in the IDS patients and to identify the risk factors associated with these errors. Knowledge of such errors will provide baseline data that will be valuable in appraising the scope of the current medication safety system and its deficits.

LITERATURE REVIEW

The Epidemiology of Medication Errors

Terminology

Medication Error: There are numerous inconsistencies among terms used to define medication errors and classify their clinical consequences[35]. In a systematic review of the characteristics of medications errors, Lisby *et al.* report that of 45 relevant studies using medication error definitions, 26 differed in wording[35]. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) is an independent body comprising 27 organizations in the United States whose goal is to promote the safe use of medications[36]. The council developed a standard definition for medication errors that they strongly encourage researchers to use: "A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use"[36]. This term is also used to define a *medication incident*[37]. This definition is widely used in studies of medication errors and is clearly reflected in the literature[15,24,32,35,38-44]. Other experts argue that a definition including failure in the treatment process is more robust[38]. Some medication errors create a large potential for harm but are intercepted before reaching the patient. Most medication errors, however, do not actually harm patients and present only a small potential for harm[40].

Adverse Drug Event: The Institute for Safe Medication Practices (ISMP) Canada endorses the following definition of an ADE: "An injury from a medicine or lack of an intended medicine". Thus, an ADE by definition includes harm caused by adverse drug reactions, overdoses, insufficient doses and drug discontinuation. This definition also includes the failure to give or take a medication[37].

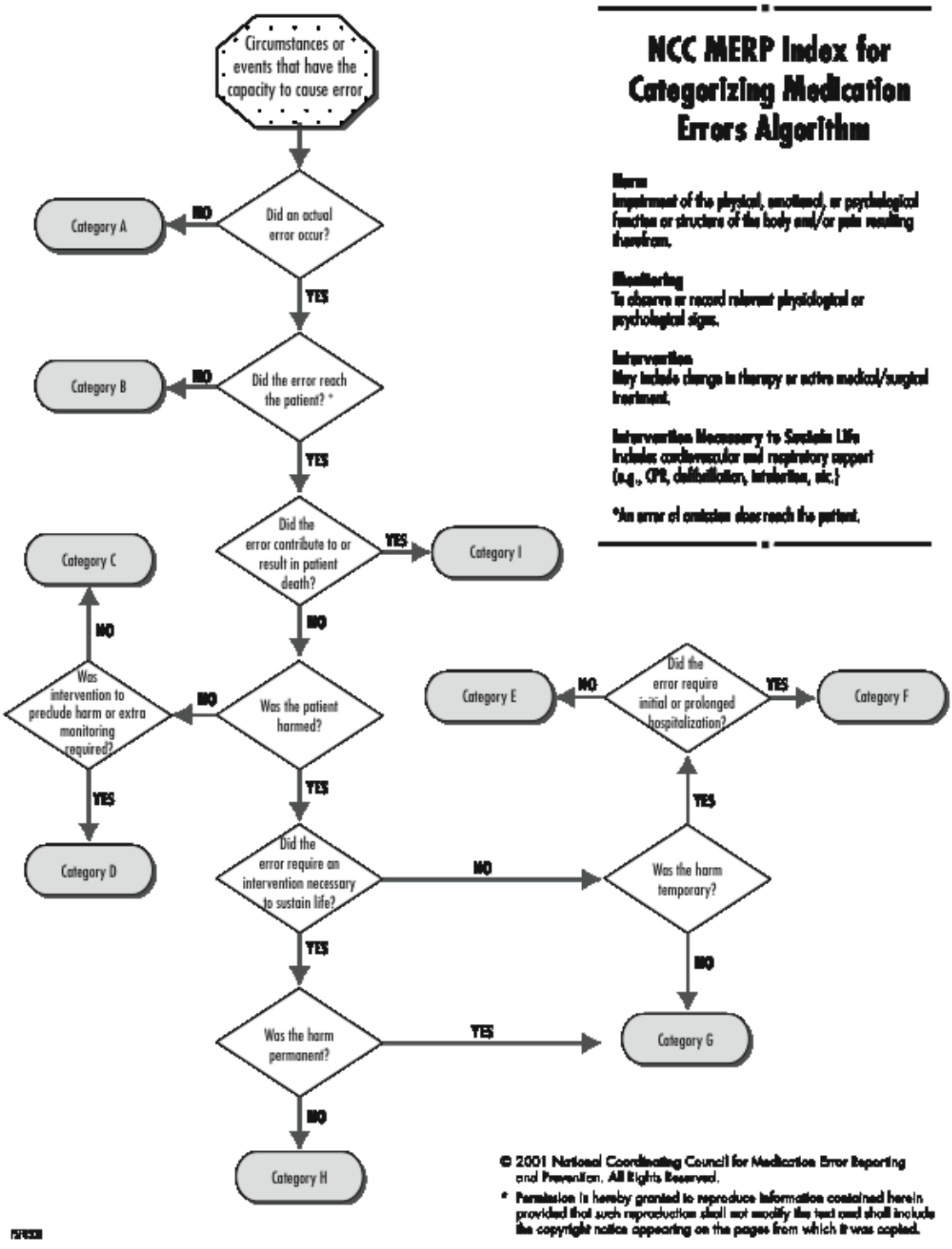
Potential Adverse Drug Event (PADE): A PADE is an incident with potential for injury related to a drug[45]. It involves a medication error that could result in an ADE, but does not because of intervention or chance[45]. These types of errors are also referred to as *near misses* or *close calls*[40,46]. An example of a PADE would be the receipt of a prescription for meperidine for a patient who is taking phenelzine, a monoamine oxidase inhibitor, and intercepting its administration. The combination of these two medications is contraindicated as it can cause hypertensive crisis[47].

Medication Safety Event: Medication safety event is an all-encompassing term including error events and non-error events (i.e. ADEs that are non-preventable). Medication safety events have been further classified as preventable ADEs, intercepted PADEs, non-intercepted PADEs, and non-preventable ADEs[46]. An example of a *preventable ADE* is administering penicillin to a patient with a documented severe penicillin allergy, which results in an anaphylactic reaction[45]. If penicillin were prescribed for a patient with a documented severe penicillin allergy, but the hypersensitivity history was detected and the drug was not administered, this would be an *intercepted PADE*. If penicillin were prescribed for a patient with a documented severe penicillin allergy and the drug was administered, but the patient did not experience a hypersensitivity reaction by chance, this would be considered a *non-intercepted PADE*. If the patient had an unknown and undocumented severe penicillin allergy and received penicillin, which caused an anaphylactic reaction, this would be a *non-preventable ADE*. The term medication error can be problematic because it excludes non-error events and may hinder the root cause analysis that is necessary to improve medication safety system deficits[46].

Classification of Severity

Depending on the rating method that is used, the severity of a medication error has been divided into two, three, four or even eighteen categories[36,39,48-51]. In general, the types of categories pertain to whether or not the error caused harm, and the impact of the harm. To standardize outcome severity, the NCC MERP developed a harm index algorithm consisting of nine discrete categories (Figure 1)[36]. Snyder *et al.*[41] validated the reliability of an adapted version of the NCC MERP algorithm that replaced the term *error* with the more comprehensive safety assessment term *event*. Inter-rater reliability for the NCC MERP algorithm was moderately high: the kappa 95% confidence interval (CI) ranged from 0.74 to 0.93 and percentage agreement 95% CI ranged from 86% to 100% for discrete index categories E-H; the kappa 95% CI ranged from 0.76 to 0.90 and percentage agreement 95% CI ranged from 69% to 90% for discrete index categories B-D[41]. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) further categorized the NCC MERP harm index into 18 subclassifications to distinguish between psychological and physical harm and include non-medical harm, such as legal, social, or economic impact[51].

Figure 1: NCC MERP Index for categorizing medication error severity algorithm.



Types of Errors in the Stages of the Medication-Use System

Prescribing and Ordering Stage: After conducting a clinical assessment, the clinician orders a medication regimen for a patient. The order may be written, verbal or electronic. Ideally, the clinician documents any change to an existing regimen in the patient's medical record. The prescribing stage has been reported to be the main source of medication errors, with incidence rates ranging from 19% to over 58%[1,52-54]. Types of prescribing errors include inappropriate dose or frequency, incorrect drug, incorrect route of administration, drug-drug interaction, drug-disease interaction, failure to review allergy history, failure to prescribe an indicated drug and prescribing to the wrong patient[6]. The main reasons for prescribing errors are inadequate knowledge about the medication or the patient, miscommunication among clinicians, and lapses in clinician performance or documentation[54-56]. The prescribing phase also includes self-prescribing, which involves the patient or caregiver's assessment of the condition and selection of therapy.

Transcribing/Documentation Stage: The transcribing stage includes the series of steps that are involved in interpreting and processing a medication order[6]. In hospital and long-term care facilities, a nurse or unit-clerk may receive the medication order and add it to the patient's medication administration record. Pharmacy staff may receive prescriptions electronically, verbally, via fax or by written hard copy. Errors in the transcribing stage may arise as a result of look-alike sound-alike drugs, poor-handwriting or incomplete information[6]. Documentation involves the accurate recording of medications in the medical records of a patient. In the hospital setting, this includes a patient's medical chart and medication administration record. In the outpatient setting, this may include the documentation of medications into an electronic database. Errors arise when there are inconsistencies between a patient's actual list of medications and the medication list that is documented in the medical record.

Drug Preparation and Dispensing Stage: The pharmacy staff is generally responsible for preparing and dispensing medications. Hospital orders and prescriptions are typically

entered into a pharmacy database. The pharmacist evaluates the therapeutic appropriateness of the medication dose, frequency, and duration and also assesses a patient's profile for CSDI, allergy and intolerance potential, and therapeutic duplication. Drug preparation may involve counting, measuring, compounding, reconstituting, repackaging and labeling. The most common error types observed during preparation and dispensing in the inpatient setting include incorrect drug, incorrect dosage, incorrect formulation and incorrect flow rate calculation[55,56]. On the other hand, outpatient errors usually involve incorrect labeling[57,58]. It is estimated that between 6% and 12% of all medication errors occur during drug dispensing[57-59]. The main reasons for these kinds of errors are staffing and workload issues, distractions, suboptimal packaging and labeling, suboptimal work environment (e.g. noisy, poor lighting) and outdated drug information resources[55,56].

Drug Administration Stage: In inpatient and long-term care settings, nurses are generally responsible for administering medications and are frequently the last professional to assess the appropriateness of the prescribed and dispensed drug[6]. The five rights, known as the right drug, right dose, right route, right time and right patient, are central to the medication administration process[6]. Types of fatal administration errors include dosing errors (mainly overdoses), incorrect drug and incorrect route[56]. Administration errors can be caused by miscommunications, miscalculations, staffing and workload issues, interruptions, rapid expansion of medical knowledge and technology and incomplete documentation[6]. Self-administration errors also occur in the outpatient setting and may include inappropriate dose, unnecessary medication, drug-drug interactions and nonadherence[6].

Drug Monitoring Stage: During the drug monitoring stage of the medication-use system, a health care professional, patient or caregiver obtains relevant data to assess a medication's therapeutic effect. The type and frequency of monitoring will depend on the nature of the illness, the care setting, the characteristics of the patient[60], and factors pertaining to the medication of interest. Drug monitoring errors observed in hospital and ambulatory care settings include inadequate laboratory monitoring[61,62], a prolonged

response or failure to respond to signs and symptoms of drug toxicity[61,62], and poor communication[63]. Failure to self-monitor responses to medications, including both therapeutic and adverse effects, may also lead to errors.

Incidence of Medication Errors

Most of the literature of medication error rates comes from hospital studies. Rates depend on the error detection method and denominator used to calculate the incidence (see *Methodological Issues*). A nation-wide study of adverse events in Canadian acute care hospitals found an overall incidence rate of 7.5%[64]. The results of this study suggest that among 2.5 million annual hospital admissions in Canada approximately 185,000 are associated with adverse events and nearly 70,000 are potentially preventable. In five studies, hospital prescribing incidence rates varied dramatically from 12.3 to 1,400 per 1,000 patient admissions[1,52,65-67]. Administration errors occur frequently, ranging from 2.4% to 11.1% per dose, excluding wrong time errors[68-72]. In two studies evaluating only intravenous medications, administration error rates were 34 and 49 per 100 doses[73,74]. There is a modest amount of research on error rates in ambulatory clinics. At least one prescribing error occurred in 21% of prescriptions in one study[75]. In an outpatient study of 12,560 Quebec patients aged 66 years or older, the rate of initiation of an inappropriate prescription per 1000 patient visits was 43.8 in a computerized clinical decision support system (CDS) group and 52.2 in the control group [relative rate=0.82; 95% CI: 0.69, 0.98][76]. Types of inappropriate prescriptions included drug-disease contraindications, drug-age contraindications, excessive duration of therapy, therapeutic duplication and drug-drug interactions. Errors have also been reported in sample dispensing. In one study, 12% of labels were missing the usual dosage and 17% of labels referred the patient to a package insert that was not present[77]. In community pharmacies, dispensing error rates have improved over time with new technology[6]. In a cross-sectional study involving 50 community pharmacies, Flynn *et al.*[58] report an overall dispensing accuracy rate of 98.3% (77 errors among 4,481 prescriptions). Although this accuracy rate appears high, it translates to a dispensing error rate of approximately 4 errors per 250 prescriptions per pharmacy per day, amounting to an estimated 51.5 million errors per 3 billion prescriptions dispensed annually in the United States[58]. Non-

adherence rates are the theme of most self-administration error studies. DiMatteo[78] reports a treatment non-adherence rate of 20.6% in a meta-analysis involving 328 studies.

Impact of Medication Errors

The clinical and economic consequences of medication errors are understudied. Current research pertains to the additional health care costs incurred by preventable ADEs. These costs reflect the injuries caused by medication errors[6]. In the hospital setting, the results of two studies suggest that hundreds of thousands of preventable ADEs occur every year in the United States[1,2]. In another study, preventable ADEs prolonged length of hospital stay by 4.6 days and cost the system an additional $5,857 per patient[5]. Dennehy *et al.*[79] found that prior ADEs accounted for 4% of all emergency department visits in one 560-bed teaching hospital. They judged that 66% of these ADEs were preventable. In one study involving ambulatory patients aged 65 years or older, preventable ADEs are estimated to cost $1,983 per patient, translating to national annual cost of $887 million in the United States[80].

The most extensive research of the rates and impact of medication errors has taken place in the hospital setting. Currently, there are gaps in the knowledge base regarding medication errors in the outpatient setting. There is a need to better define the nature of medication errors that occur in the ambulatory care domain.

Methodological Issues

Interpreting the literature of medication errors can be challenging. In addition to the lack of consensus on the definition of a medication error, there are a number of other methodological issues. For example, methodological problems can arise both from variability in methods used to detect medication errors and from which the denominator is chosen[38]. Consequently, published incidence rates can vary dramatically. The most common error detection methods include chart review, direct observation, computerized monitoring and voluntary reporting[6]. Review of hospital records and prescriptions is a relatively inexpensive and easy method for identifying errors. However, studies involving only chart review may fail to identify medication errors that occur in the

dispensing and administration stages of the medication-use system[38]. In a randomized controlled study involving pharmacotherapy consultations, Jameson and VanNoord report that 73% of drug-related problems were discovered only during patient interview[81]. Flynn *et al.* attest that the most reliable method for measuring error incidence is to directly observe and compare prescribed and administered doses[82]. Unfortunately, this method is likely to be expensive and is not feasible for all patient settings. Spontaneous reports of medication errors may be evaluated, although it is difficult to make accurate estimations of prevalence because of the large potential for reporting bias and the tendency for serious underreporting[38]. The evaluation of the denominator is equally difficult and adds to the heterogeneity of the medication error literature. Error rates can be estimated in several ways such as errors per patient, errors per admission, errors per medication order, errors per dose, errors per opportunity and errors per person-time units. Other difficulties may arise when evaluating error rates from different stages in the medication-use system: errors which occur early in the medication-use system tend to be more easily identified and intercepted than those which occur later and are thus less likely to actually harm patients[38]. The misinterpretation of error rates can create difficulty in evaluating the relevance of a problem and in measuring the effectiveness of error reduction strategies. When interpreting the literature of medication errors and comparing various studies, it is important to be clear on outcome definitions, error detection techniques and methods for calculating error rates.

PLHA are Vulnerable to Medication Errors

PLHA are at a particularly high risk of experiencing medication errors for the following reasons:

Clinically significant drug-drug interactions: Advancements in medicine have improved survival rates in patients with HIV[83]; however, as patients live longer they are at an increasing risk of developing comorbidies that require pharmacotherapy. Patients who receive more medications are at a higher risk of experiencing drug-drug interactions. A drug-drug interaction is deemed clinically significant when it alters the intended therapeutic outcome and consequently reduces clinical effectiveness or

increases/intensifies adverse effects[84]. Several ARV drugs, including the protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and chemokine (C-C motif) receptor 5 (CCR5) antagonist drugs act as substrates, inducers and/or inhibitors of the cytochrome P450 enzyme (CYP) system[84]. This system is made up of major enzymes that are involved in drug metabolism and biotransformation[85]. Thus, there is an increased risk of drug-drug interactions when other medications that are metabolized by CYP enzymes are coadministered with ART. Any time a change is made to a patient's medication regime, an evaluation of drug-drug interactions is critical. In a recent survey, Evans-Jones *et al.* report that physicians working in an HIV clinic identified only 36% of CSDI[86]. CSDI create a great potential for medication errors in patients receiving antiretrovirals.

Dosing issues involving renal and hepatic insufficiency: It is estimated that 30% of patients with AIDS have kidney disorders associated with HIV infection, which in certain cases can lead to chronic renal insufficiency[87]. Moreover, as people age, renal function declines[88]. The elimination of certain ARV medications can be considerably affected by renal impairment[87] and it is important to monitor patients closely for changes in renal function. Medication errors can arise when ARV doses are not adequately adjusted for a patient's renal function.

In PLHA there is a high prevalence of chronic hepatitis caused by either hepatitis C (HCV) or hepatitis B (HBV) infection[89]. Chronic liver disease can lead to changes in hepatic function. The impact of hepatic insufficiency on ARV pharmacokinetics is variable and often unpredictable[90]. In severe liver disease, therapeutic drug monitoring may be necessary to ascertain adequate drug exposure and to minimize toxicities. Medication errors can occur from overdosing or underdosing ARV drugs in patients with hepatic impairment.

Failure to reconcile medication profiles: Patients with HIV infection exist in a healthcare delivery system that is becoming increasingly complex. Multiple providers may be involved in managing a patient's pharmacotherapy issues. Patients may transition

from ambulatory care to hospital to long-term care or home care. Patients may collect prescriptions from more than one community pharmacy. They may self-prescribe over-the-counter (OTC) and natural health products. Inaccurate or incomplete medication histories can cause medication errors that result in patient harm. Inconsistencies may exist among the sources that document a patient's medication history (e.g. pharmacy records, clinic databases, prescription bottles) and what the patient actually takes. The most commonly observed medication discrepancies include patients taking a medication for which there is no documentation (i.e. omission errors)[91-94], patients not taking documented medications[91,93,95], and dosing inconsistencies[91,95].

Self-prescribing of non-prescription medications and complementary and alternative medicine use (CAM): It is estimated that over 300,000 OTC products are commercially available in the United States[96]; non-prescription medication use is unarguably ubiquitous. The use of complementary and alternative medicine (CAM) is common among PLHA, the prevalence ranging from 40% to 80%[97-109]. In one study, Milan *et al.*[107] report that PLHA were more likely than patients without HIV infection to take dietary supplements and prescription medications concomitantly within the past 6 months [75% versus 43%; $p<0.002$]. In the same study, the results of a multivariate analysis demonstrate that HIV infection was the only factor that was significantly associated with daily dietary supplement use [OR 3.1; 95% CI: 1.3, 7.7]. Although there is a scarcity of published studies describing non-prescription medication errors, there is emerging evidence for OTC-related CSDI and drug-disease interactions[6]. Frequent self-prescribing and CAM use in PLHA therefore may increase the risk of experiencing medication errors.

Look-alike, sound-alike medications: A number of case reports describe administration and dispensing errors as a result of look-alike, sound-alike drugs such as nevirapine (Viramune) and nelfinavir (Viracept)[22], zidovudine (AZT) and azathioprine[10,11,110,111], Combivir and Combivent[32], stavudine and stelazine[112], and lamivudine and lamotrigine[113]. In addition, the Institute for Safe Medication Practices (ISMP) published a list of confused drug names[114] which includes name pairs that have been involved with

medication errors and/or those which are present on the Joint Commission's list of look-alike, sound-alike names. Other name pairs noted in the ISMP's list include Kaltra and Keppra, Kaletra and Kapidex, ritonavir and Retrovir, indinavir and Denavir, and saquinavir and Sinequan[114].

Suboptimal adherence to ART: One of the key issues relating to HIV care is that patients must take ARV medications accurately and consistently in order to experience the greatest benefit of ART[115], that is, to maximally and durably suppress the HIV viral load and to restore/preserve immunologic function[116]. PLHA make a lifelong commitment to taking ART, which comes with a wide range of challenges. Adherence is defined as the degree to which a person's behaviour is consistent with agreed recommendations from a healthcare provider[117]. Adherence to ART is necessary to achieve therapeutic success[118]. Higher rates of adherence have been associated with HIV viral suppression, lower rates of drug resistance, increased survival and improved quality of life[116]. The self-reported adherence rates of most patients on ART are estimated to be between 56% and 88%[119]. Unfortunately, even 88% is an inadequate rate; the literature indicates that adherence rates of greater than 80-95% are needed to attain goals of therapy[118]. Poor adherence can be related to low levels of literacy, cognitive impairment, language issues, social stigma, active drug use, depressive symptoms and financial constraints[34,117,120]. One of the most significant predictors of non-adherence to ART is a patient's treatment competency, defined as having incorrect beliefs about medication, their disease, and lower optimism of treatment efficacy[121]. Limited data suggest that the prevalence of patient-related ARV medication errors is clinically important[34,122,123].

Previous Studies of Medication Errors in PLHA: Hospital Setting

There is increasing evidence that prescribing errors involving ARV medications are common during hospitalization[8,9,13,15,16,23,24,27,31]. Carcelero *et al.*[9] prospectively evaluated the medication profiles for all inpatients who were prescribed ART over 1 year. The authors identified 60 ARV medication errors among 247 admissions of patients receiving ART. The most common error types were inappropriate drug combinations (33%), dose-related error (28%) and dose omission (15%). The results of a multivariate analysis

indicate that the following factors were associated with an increased risk of ARV errors: renal impairment [OR 3.95; 95% CI: 1.39, 11.23], treatment with atazanavir [OR 3.53; 95% CI: 1.61, 7.76] and admission to a unit other than an infectious diseases unit [OR 2.50; 95% CI: 1.28, 4.88]. Conversely, treatment with an NNRTI was associated with a decreased risk of ARV errors [OR 0.33; 95% CI: 0.13, 0.81].

In another prospective study, Pastakia *et al.*[24] evaluated ARV prescribing errors over a 3-month period. The authors identified 82 errors among 68 patients receiving ART. In 56% of patients, the error had the potential to cause moderate or severe discomfort or clinical deterioration. Univariate analyses suggested that atazanavir use increased the risk of error during hospitalization [RR 1.69; CI: 1.03, 2.78]. The authors speculate that this finding was likely due to the concomitant use of proton-pump inhibitors and atazanavir, which was a contraindicated drug combination at the time this study took place[8]. Furthermore, patients receiving an ARV drug that required conversion to a medication of equivalence on hospital formulary significantly increased the risk of having more than one error [RR 1.95; CI: 1.25, 3.04].

Snyder *et al.*[27] determined the incidence of ARV and opportunistic infection (OI)-related medication errors in hospital admissions over a 2-month period. They identified 69 of such errors in 20 of 26 (77%) patients with an estimated incidence of 2.7 errors per patient admission. The most common error types included missing doses (20%), overdosing (13%), therapy omission (13%), and drug-drug interaction (12%). The main causes of the errors were lack of medication knowledge, failure to reconcile home or transfer medications, inappropriate drug information in the decision support software, transcription miscommunication and overlooking dispensing alerts in the decision support software. Eighty percent of these errors occurred during the prescribing stage.

In a retrospective study, Mok *et al.*[23] evaluated the type and frequency of drug-related problems in hospitalized patients with HIV infection. They reviewed the medical records of 83 patients and discovered 176 errors. The most common drug-related problems included inappropriate dosing (32%), drug-drug interactions (26%) and incomplete ART

(20%). The authors report that there was no significant difference in the mean length of stay between patients with or without drug-related problems. However, admission by physicians who were not infectious disease specialists was independently associated with having at least one drug-related problem during hospitalization [OR 3.83; 95% CI: 1.08, 13.54].

Heelon *et al.*[16] retrospectively identified ARV prescribing errors in hospitalized patients over a 6-month period and compared the effect of a clinical pharmacist's interventions on the duration of the errors. Among 199 admissions of patients receiving ART, a total of 73 errors were confirmed, the most common error types were incomplete ARV regimen (45%) and incorrect dosage (30%). The median length of time until an error was corrected was significantly shorter during the intervention phase than the pre-intervention phase [15.5 hours; range 1-216, versus 84 hours; range 24-7584; $p<0.0001$]. More information on the severity of these errors and the inter-quartile ranges (IQR) for the length of time would be useful in assessing the full impact of the pharmacist intervention.

Rastegar *et al.*[8] reviewed the medical records of patients with HIV infection admitted to hospital over a 1-year period. They identified 89 errors per 209 admissions of patients receiving ART. The most common error types included inappropriate dosing (49%), inappropriate drug combination (15%), and incomplete ARV regimen (17%). Results of a multivariate analysis indicate that renal insufficiency, defined as a glomerular filtration rate (GFR) less than 60 mL/min, was the only factor that was independently associated with an ARV medication error [OR 5.18; CI: 2.61, 10.28]. The authors describe a PADE in a patient who received lopinavir/ritonavir and simvastatin concurrently and experienced increased liver enzyme levels until simvastatin was discontinued.

Edelstein and Wilson[13] describe incorrect dosing intervals (BID written as 10:00 am and 6:00 pm or TID written as 10:00 am, 2:00 pm and 6:00 pm) in 100% of the ARV hospital orders that they randomly selected for review. Furthermore, only 27% of orders had appropriate food and fasting state requirements.

Purdy *et al.*[31] report 108 prescribing errors in ARV medications among 1618 of admissions of patients receiving ART over the 34-month study period. The most common error types detected included incorrect dosing (81%) and incomplete ART (7%) and inappropriate drug combinations (6%). In this study, the incidence of ARV prescribing errors increased from 2% of admitted patients prescribed ART in 1996 to 12% of admitted patients prescribed ART in 1998. The authors attribute this finding to the increasing complexity of ARV regimens.

Gray *et al.*[15] evaluated ARV medication errors using a national voluntary reporting database. They found that the most common error types reported were inappropriate dosing (38%) and incorrect medication (32%). Of the 400 reported errors, 49% reached the patient, but less than 1% of errors were associated with patient harm.

Previous Studies of Medication Errors in PLHA: Outpatient Setting

Fewer reports describe ARV medication errors in the outpatient domain[12,17,18,30,32,33]. Hellinger and Encinosa[18] analysed the cost and frequency of ARV prescribing errors using insurance claims data. They found that the prevalence of inappropriate ARV drug combinations in 2005 was three times higher than in either 1999 or 2000 (5.9% versus 1.9%). They attribute this finding to patients receiving atazanavir and tenofovir without ritonavir, which they refer to as a "boosting error". When atazanavir is given without ritonavir, tenofovir may reduce the minimum drug concentrations of atazanavir by 23-40%[117]. Current guidelines recommend administering ritonavir with atazanavir when combining with tenofovir to ensure adequate drug plasma concentrations[117]. The authors note a trend towards a higher risk of opportunistic infections in patients who experienced boosting errors versus those who did not [OR 1.28; 95% CI: 0.92, 1.64]. In addition, the costs incurred by patients with boosting errors were 21.5% higher than those who did not experience a boosting error. In an earlier study involving only the data from 1999 and 2000[17], the authors found that patients receiving a PI and simvastatin concomitantly were 17 times as likely to be diagnosed with myopathy, polyneuropathy or myositis [OR not reported; p=0.001]. Moreover, patients who took an inappropriate drug combination tended to be more likely to become hospitalized [OR 2.28; 95% CI: 0.85, 6.11].

Hulgan *et al*.[19] analyzed the computerized prescription records of 3,448 patients receiving PI therapy between 1996 and 2002. Among patients receiving concurrent treatment with a PI and a statin, the proportion of contraindicated combinations decreased from 42.0% to 20.8%, reflecting updated treatment guidelines for drug combinations to avoid. However, the authors remark that the proportion of patients receiving contraindicated PI and statin combinations remains unacceptably high.

DeLorenze *et al.*[12] evaluated the pharmacy records of 5,473 outpatients with HIV infection. They found that the incidence of dosing errors was 9.80 per 1000 new prescriptions (95% CI: 8.66, 10.2) and the incidence of contraindicated combinations of medications was 9.51 per 1000 new prescriptions (95% CI: 5.72, 14.10). Age greater than 50 years was associated with a significantly higher risk of a contraindicated drug combination when compared to age less than 40 years (OR 1.94; 95% CI: 1.29, 2.93], whereas black race was associated with a significantly lower risk of the same outcome [OR 0.35; 95% CI: 0.17, 0.74].

In another retrospective study, Willig *et al.*[30] investigated the frequency and factors related to nucleoside reverse transcriptase inhibitor (NRTI) dosing errors in an outpatient HIV clinic. They identified 53 (6%) incorrect doses among 907 NRTI prescriptions. Older age [OR 1.75 per 10 years; 95% CI: 1.28, 2.38 per 10 years], minority race or ethnicity [OR 2.69; 95% CI: 1.37-5.26] and the use of didanosine [OR 11.51; 95% CI: 5.99, 22.10] were significantly associated with NRTI dosing errors.

In a study involving outpatient injection drug users (IDU), Arnsten *et al.*[34] assessed patient errors in ARV dosing, defined as daily doses that were inconsistent with current guidelines for standard or any alternative ARV prescriptions. Among 636 patients, medication errors were made by 346 (54%). In univariate analyses, an HIV viral load < 400 copies/mL and a CD4+ T cell count $\geq$ 200 cells/mm^3 were associated with a lower likelihood of experiencing a medication error [OR 0.69; 95% CI: 0.49, 0.96 and OR 0.44; 95% CI: 0.30, 0.63, respectively]. In a multivariate analysis, medication errors were

independently associated with non-Hispanic black race [OR 2.41 95% CI: 1.17, 4.96] and Hispanic race [OR 3.08; 95% CI: 1.38, 6.88] (reference: non-Hispanic white), depressive symptoms [OR 1.35; 95% CI: 1.09, 1.68], higher self-efficacy for safer drug use [OR 0.80; 95% CI: 0.69, 0.93] and positive attitudes towards HIV medications [OR 0.44; 95% CI: 0.28, 0.69].

Tourret *et al.*[28] evaluated the frequency of ARV prescribing errors in PLHA undergoing hemodialysis. They detected 187 (59%) inappropriately prescribed ARV medications of 317 ARV prescriptions. Patients who received an insufficient PI dose had more severe HIV disease that was characterized by a higher mean HIV viral load [2.9 $\pm$ 1.3 log copies/mL versus 2.2 $\pm$ 0.9 log copies/mL, $p<0.005$], a higher rate of AIDS diagnosis [57% versus 27%; $p<0.006$] and a trend towards having a lower mean CD4+ T cell count (271 $\pm$ 149 cells/mm^3 versus 345 $\pm$ 188 cells/mm^3; $p<0.06$]. Furthermore, patients who received an insufficient PI dose had a lower 2-year survival rate [79.5% $\pm$ 7.5% versus 95.4% $\pm$ 2.6%; $p<0.02$]. There were no significant differences in the 2-year survival rates between patients who received an insufficient NRTI dose and those who did not. It is important to note the potential for confounding by indication: patients who initially had a poorer prognosis could have been prescribed a lower PI dose.

Zangeneh *et al.*[33] reviewed medical charts to evaluate the frequency of ARV prescribing errors that occurred between January 1 and December 31, 2007 in both inpatient and outpatients. They identified 24 errors among 514 charts reviewed. The most common error types included inappropriate dosing in renal insufficiency (54%) and contraindicated drug combinations (46%).

Ungavarski *et al.*[29] reviewed a convenience sample of homecare patient records to quantify errors in dosage frequency. The authors identified incorrect dosing schedules in 36 (39.6%) of 91 patients. There were prescribing errors in 22 (50%) of indinavir orders, 7 (24.3%) of saquinavir orders and 2 (22.2%) of ritonavir orders. They also found prescriptions for PI monotherapy in 3 patients.

Cocohoba and Dong[32] reviewed ARV medication errors that were voluntarily reported by patients and clinicians in an HIV clinic over a 3-year period. They classified these errors using the NCC MERP Index[36]. Thirty-one (97%) of the reported errors reached patients, although the majority of errors did not result in obvious harm (97%) and did not require any intervention (88%). Lapses in the community pharmacy or clinic systems to authorize and dispense ARV refills on time accounted for 63% of the errors. The remaining errors were associated with the prescribing and self-administration stages of the medication-use system.

In summary, a number of studies describe medication errors among outpatient PLHA that have resulted in true or potential harm. Possible risk factors for medication errors include older age, minority race (although black race is also associated with a lower risk of errors), depressive symptoms, and certain medications such as atazanavir and didanosine. The focus of previous research relates to errors in the prescribing stage. Only one study described patient-related medication errors in outpatient PLHA and this involved a specific population; namely, IDU. A study involving pharmacist-conducted interviews would be beneficial in identifying medication errors that occur not only at the prescribing stage, but also the transcribing/documentation stage (e.g. omission errors) and the self-administration stage (i.e. patient-related errors).

OBJECTIVES

The general objective of this project was to characterize medication errors in an HIV ambulatory care setting.

The specific objectives of this project were as follows:

1. To quantify frequency of medication errors in the study population.
2. To evaluate the type and severity of medication errors in the study population.
2. To assess the association of error frequency with several covariates.
3. To assess the association of error severity with several covariates.

METHOD

Study Design

This was a hypothesis-generating study that was cross-sectional by design.

Study Setting and Population

The DEFEAT Study took place at the IDS at the Montreal Chest Institute. The IDS is one of the largest university-affiliated, HIV outpatient clinics in Canada, serving over 1,600 patients per year. There is a great diversity in the patient population at the IDS, including IDU, men who have sex with men (MSM) and refugees from other countries. Primary and specialty care are provided through an interdisciplinary approach including medicine, nursing, pharmacy, social work, nutrition, psychology and pastoral services. Since 1989, the IDS team has managed information on demographics, comorbidities, HIV risk factors, medication use and other clinical data through a comprehensive database. The database is used clinically to determine a patient's living record of mediations. Datasheets are printed from the database and updated during a patient's clinic visit. The reconciliation of medication discrepancies between the datasheet and the patient's current medication list is generally the responsibility of the physician, but is also carried out by the clinic pharmacists or nurses when they meet with patients.

Selection of Participants

IDS patients who were HIV-seropositive, receiving ART and who had at least two clinic visits during the previous twelve months met study inclusion criteria. By simply reviewing the eligibility of odd-numbered patients on the daily clinic appointment list, eligible patients were selected at random during their medical visits and invited to participate. Refusals were recorded in order to assess selection bias. Several attempts to reach patients by phone or intercept patients at clinic visits were made to reschedule those who missed or cancelled study visits. Unattainable patients were deemed lost to follow-up. Participants received $20 to compensate for parking and/or childcare expenses. Recruitment for the DEFEAT Study began in March 2009 and enrolment

concluded in July 2010. The McGill University Health Centre Research Ethics Board approved this project.

Data Collection

Screening Visit

After providing informed consent, patients attended a screening visit with a research assistant. During this visit, patients completed a questionnaire to provide demographic and clinical data and community pharmacy contact information.

Study Visit

Patients returned to the clinic approximately one week later to attend the study visit. They were instructed to bring all medications to this visit, including prescription drugs, OTC and natural health products, dietary supplements, inhalers, injections, etc. The research assistant contacted the community pharmacists in advance to request a faxed copy of each patient's most current outpatient pharmacy profile. At the start of the interview, patients completed the Simplified Medication Adherence Questionnaire (SMAQ)[124] to assess adherence to ART. Clinical pharmacists interviewed patients to obtain the best possible medication history (BPMH)[125]. Interviews were semi-structured and included open-ended questions (e.g. "Tell me about how you take this medication?") as well as prompting questions for non-prescription drugs (e.g. "What do you take when you have a headache?") and unique dosage forms (e.g. "Tell me about your use of eye drops, inhalers, patches, sprays and topical products?"). Medications that the patient took on an as-needed basis were included if the patient reported using them at any time during the past year. The pharmacists were permitted to access the clinic and community pharmacy medication lists to obtain the most accurate medication history. In addition, the pharmacists assessed how the patient took each medication with respect to dose, frequency and food requirements. A typical interview lasted between 30 and 60 minutes, depending on the complexity of the patient's medication history.

Assessment of Covariates

To assess factors associated with the frequency and severity of medication errors, the research team collected demographic, clinical, medication, pharmacy and adherence data

as well as information on alcohol, tobacco and recreational substance use. Demographic characteristics included age, gender, race, country of origin, first language, level of education, immigration status and neighbourhood. Clinical characteristics included HIV risk factors, time since HIV diagnosis, most recent viral load, most recent CD4+ T cell count, CD4+ T nadir, comorbidities, history of hospitalization during past year, whether a patient saw more than one physician during past year and GFR. Demographic and clinical characteristics were ascertained using three sources: the patient during the screening visit, the medical chart and the clinic database. The BPMH was confirmed as described above using multiple sources: the patient during the study interview, pill bottles, pharmacy records and the clinic database. As mentioned earlier, the pharmacists administered the SMAQ to assess adherence to ART. The pharmacists asked study patients about alcohol use (i.e. yes/no and number of drinks per week), tobacco use (i.e. yes/no, number of cigarettes per day), marijuana use (i.e. yes/no, number of joints per day) and other recreational substance use during past year (i.e. yes/no, type, frequency) during the study visit.

Error Ascertainment (Outcome Assessment)

The main outcomes of interest were the number of errors per patient and medication error severity. For the former outcome, only errors that reached the patient were included in the analysis. Two pharmacists, each with more than two years of clinical experience in HIV, independently evaluated the patients' medication profiles for errors. The pharmacists compared the clinic and community pharmacy medication histories to the BPMH to detect discrepancies and identify errors for each patient. A medication error was defined using the aforementioned definition of the NCC MERP Index for Categorizing Medication Errors[36]. Pharmacists used all available information sources (e.g. the most recent publication of the Department of Health and Human Services HIV Guidelines[117], HIV Medication Guide[126], Micromedex® Healthcare Series[127], University of Liverpool HIV drug interaction database[128] and Toronto General Hospital HIV drug interaction tables[129]). Pharmacists evaluated the drug combinations for CSDI. The definition of a CSDI was limited to drug combinations that were contraindicated (e.g. ritonavir and fluticasone), those which necessitated a dose adjustment (ritonavir and sildenafil 100 mg prn) and/or therapeutic drug monitoring of one or both medications

(e.g. unboosted atazanavir and tenofovir) according to expert guidelines on drug-drug interaction management. Pharmacists approximated each patient's GFR by using the Cockcraft-Gault equation[88]. For patients with renal impairment, pharmacists determined if medication doses were adjusted according to published recommendations. Pharmacists additionally evaluated medication profiles for therapeutic duplication, incomplete ARV regimen, indication for OI prophylaxis, incorrect dosage, incorrect schedule, omission errors (i.e. medications that the patient was taking which were not documented in the clinic or community pharmacy lists) and insertion errors (i.e. medications that were documented in the clinic or community pharmacy list that the patient was not actually taking). Poor adherence to drug therapy was considered to be a medication error only when it pertained to an incorrect dose, incorrect frequency, incorrect food requirements or the complete failure to take a prescribed medication. After identifying medication errors, the pharmacists classified each error by severity according to the NCC MERP algorithm[36] (Figure 1). Any inconsistency or difference between the BPMH and the clinic or community pharmacy medication list was classified as a Category A error according to the NCC MERP Index. The pharmacists reviewed the results of each medication error evaluation for concordance. In cases of discordance, the pharmacists had a discussion to reach a consensus.

Statistical Methods

To characterize the study population, descriptive statistics (medians, IQRs) and frequency distributions (counts, percentages) were presented for the continuous data (e.g. age, time since HIV diagnosis, number of concomitant medications) and the categorical data (gender, race, HCV coinfection), respectively. Poisson models were fit to investigate which covariates were predictive of a patient experiencing a higher number of errors. Only errors that reached the patient (i.e. Category C or greater) were included in the Poisson model. Proportional odds models were fit to investigate which covariates were predictive of a prescription being associated with a more severe error. The point estimates and the 95% confidence intervals (CI) were expressed as mean rates for the Poisson model and odds ratios (ORs) for the proportional odds model. The analyses were performed using STATA statistical software version 11.1[130] and R version 2.12.2[130,131].

Poisson Model

Univariate and multivariate Poisson models were fit to evaluate the association of demographic, clinical, medication, pharmacy, adherence and substance use covariates with the outcome *number of medication errors that reached the patient* for a given patient. The outcome included only medication errors that reached patients because the associated risk factors for these errors were considered to be the most clinically relevant. The *number of errors* outcome represents count data and therefore Poisson regression is an appropriate choice rather than collapsing the counts to into a categorical outcome which may lead to information loss and decreased statistical power[132]. Robust ("empirical" or sandwich) standard errors were used in calculating CIs.

Univariate Poisson models were fit to estimate the crude log-odds of experiencing a higher number of medication errors. A multivariate model was first created using covariates that demonstrated significant associations in the univariate analyses as well as variables that were determined *a priori* to be clinically significant. Bayesian Model Averaging (BMA) using the Bayesian Information Criterion (BIC) was also employed in order to identify which covariates were included in the best models and to investigate confounding. This approach accounts for the model uncertainty in the variable selection problem by averaging over the best models according to approximate posterior model probability[133]. A parsimonious model was then constructed through the manual elimination of covariates that did not significantly ($p \leq 0.10$) contribute to the model and those which had a low posterior probability (< 30%) of being included in the best models according to the BIC. The final multivariate model included the number of concomitant medications, years since HIV diagnosis, allophone patients (i.e. patients whose first language was neither English nor French), anti-infectives, cardiovascular disease, erectile dysfunction medications, and poor adherence (i.e. patients who had missed ≥ 3 doses of ART during past week).

Proportional Odds Model

Univariate and multivariate proportional odds models were fit to evaluate the association of demographic, clinical, medication, pharmacy, adherence and substance use covariates with the outcome *medication error severity* for a given prescription. The proportional

odds model included four categories of increasing severity; namely, no error, errors that did not reach the patient (i.e. Categories A or B), errors that reached the patient, but required no intervention (i.e. Category C), and finally, errors that reached the patient, required intervention, with or without causing patient harm (i.e. Category D or E). An ordinal regression model was chosen to preserve the integrity of the ordered medication error severity data. This method provides a more sensitive and powerful analysis than would be possible by running a series of binary logistic regressions[134]. The proportional odds model is appropriate for cross-sectional studies involving an ordinal outcome and it provides a measure of association that is readily interpretable across all dichotomizations of the outcome[134]. Multinomial regression was considered, however the natural ordering of the severity data would be lost in using this method.

Univariate proportional odds models were fit to estimate the crude ORs of experiencing a more severe medication error. A multivariate model was first created using covariates that demonstrated significant associations in the univariate analyses as well as variables that were determined *a priori* to be clinically significant. A parsimonious model was then constructed through the manual elimination of variables that did not significantly ($p \leq 0.10$) contribute to the model. The final multivariate model included anti-infectives; chemotherapy; erectile dysfunction medications; inhalers and intranasal products; natural health products; non-opioid analgesics; number of day hospital visits; number of OTC products; obtaining prescriptions from more than one pharmacy; psychotropic medications; vitamins, minerals and electrolytes; and years since diagnosis. Robust variance estimation was used for all ordinal regression analyses to account for the correlation of data contributed by the same patient.

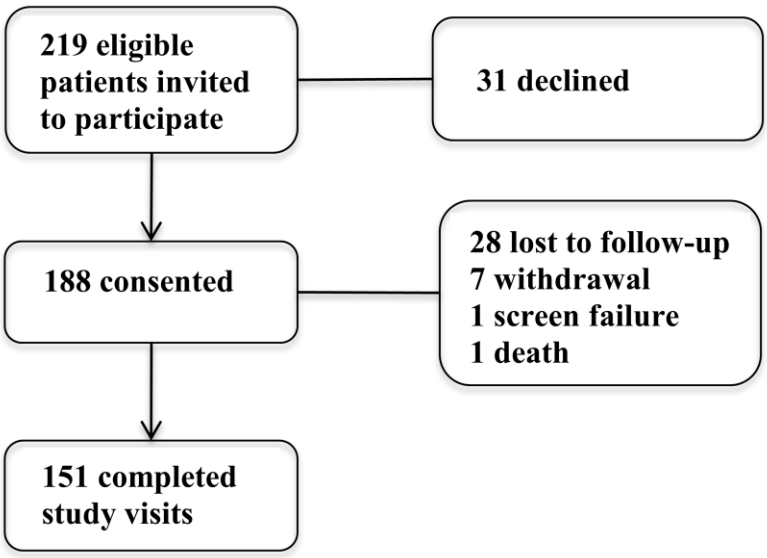
RESULTS

Characteristics of Patients

Among the 219 eligible patients who were invited to participate in the study, 188 agreed and 31 declined (Figure 2). Of the 31 patients who declined to participate, 14 (45%) were women and 19 (61%) were born outside Canada. Documented reasons for refusing to participate included being too busy (n=6), having a recent stroke (n=1), having

language barriers (n=1), and being institutionalized without access to medication (n=1). Of the 188 patients who provided informed consent, 7 later withdrew from study (6 of whom reported being too busy), 1 died, 1 failed to meet study criteria at time of study visit, and 28 patients were deemed lost to follow-up (i.e. did not return for the study visit with the pharmacist and were unattainable by telephone to reschedule). Thus, 151 patients completed study visits and were included in the analysis. Those who refused to participate tended to be slightly younger in age [median=46 (IQR: 35-51) years versus median=48 (IQR: 41-55) years] and more recently diagnosed with HIV [median=10 (IQR: 5-15.5) years versus median=13 (IQR: 5-18) years]; the proportion of women who refused to participate tended to be higher than those who participated [0.452 versus 0.185]. Figure 2 is a flow diagram illustrating inclusion in the present analysis.

Figure 2: Flow diagram of the number of subjects included in the analysis of the DEFEAT Study.



Patient characteristics are presented in Table 1. Patients were a median age of 48 (IQR: 41-55) years and were diagnosed with HIV a median of 13 (IQR: 5-18) years ago. The median CD4+ T cell count at the time of study was 365 (IQR: 237-530) cells/mm^3 and HIV viral loads ranged from < 50 copies/mL to 120,000 copies/mL at the time of study. Most patients were men (n=123, 81.5%), of white race (n=87, 57.6%), had high school

education or greater (n=142, 94.0%) and had HIV viral loads below 50 copies/mL (n=133, 88.1%) at the time of study. The median number of comorbidities was 4 (IQR: 2-6) and the median number of concomitant medications, including prescription and non-prescription medications, was 9 (IQR: 5-13). Men who have sex with men was the most commonly reported risk factor (n=95, 62.9%) followed by heterosexual (n=37, 24.5%). Twenty (13.3%) patients were coinfected with HCV. During the past 12 months, 63 (41.7%) patients reported visiting more than one physician and 15 (9.9%) obtained prescription medications at more than one pharmacy. Among first languages, 74 (49.0%) patients were francophone, 28 (18.5%) were anglophone and 49 (32.4%) were allophone. Sixty-seven (44.4%) participants were born outside of Canada and 22 (14.6%) had refugee status. Regarding substance use during the past year, 56 (37.1%) patients reported tobacco use, 107 (70.9%) reported alcohol use, 37 (24.5%) reported marijuana use and 14 (9.3%) reported other recreational drug use. Tobacco users smoked a median of 12.3 (IQR: 6.0-24.5) cigarettes per day; alcohol users drank a median of 2.0 (IQR: 0.5-5.0) alcoholic beverages per week.

Table 1: Patient demographics (n=151). HIV-RNA is expressed as range (IQR).

Characteristic	Count (%) or Median (IQR)
Age (years)	48 (41-55)
Male	123 (81.5)
Men who have sex with men	95 (62.9)
Heterosexual	37 (24.5)
History of injection drug use	14 (9.3)
Endemic risk factor	32 (21.2)
Blood transfusion as mode of transmission	4 (2.7)
Mother-to-child-transmission as mode of transmission	1 (0.7)
Black race	33 (21.9)
White race	87 (57.6)
Other race	31 (20.5)
Anglophone	28 (18.5)
Francophone	74 (49.0)
Allophone	49 (32.4)
Born outside of Canada	67 (44.4)
Refugee status in Canada	22 (14.6)
High school education or greater	142 (94.0)
Years since HIV diagnosis	13 (5-18)
HIV-hepatitis C coinfection	20 (13.3)
Number of comorbidities	4 (2-6)
History of cardiovascular disease	28 (18.5)
History of diabetes mellitus	12 (8.0)
History of dyslipidemia	45 (29.8)
History of renal disease	13 (8.6)
Tobacco use during past year	56 (37.1)
Alcohol use during past year	107 (70.9)
Marijuana use during past year	37 (24.5)
Other recreational drug use during past year	14 (9.3)
Other recreational drug use during past month	10 (6.6)
Number of concomitant medications	9 (5-13)
Hospitalized during past year	45 (29.8)
Visited more than one physician during past year	63 (41.7)
Prescriptions from > 1 pharmacy during past year	15 (9.9)
Patient takes investigational medication	7 (4.6)
Missed $\geq$ 3 doses of ART during past week per SMAQ	5 (3.3)

Characteristic	Count (%) or Median (IQR)
Missed $\geq$ 2 days of ART during past 3 months per SMAQ	23 (15.2)
HIV-RNA (copies/mL)	49-120000 (49-49)
HIV-RNA < 50 copies/mL	133 (88.1)
CD4+ T cell count (cells/uL)	365 (237-530)
Nadir CD4+ T cell count (cells/uL)	237 (127-344)
Glomerular filtration rate (mL/min)	87.2 (71.8-102.6)
Glomerular filtration rate < 50 mL/min	8 (5.3)

Non-Prescription Medications and Vitamin Use Among Patients

Non-prescription medication use was common in study patients (Table 2). One hundred and ten patients (72.9%) reported OTC product use. Nearly half of patients were taking vitamin, mineral or electrolyte medications either by prescription or OTC. Nearly one third of patients reported using natural health products, such as herbal remedies, Chinese medicines, probiotics and dietary supplements.

Table 2: Non-prescription medication and vitamin use among patients (n=151)

Characteristic	Count (%)
Over-the-counter product use	110 (72.9)
Vitamin, mineral or electrolyte use	75 (49.7)
Natural health product use	46 (30.5)
Any non-prescription medication or vitamin use	125 (82.8)

Adherence to ART

The SMAQ questionnaire detected that 101 (66.9%) of patients reported some kind of suboptimal adherence to ART at some stage during treatment, including forgetting to take medications, being careless about taking medications or stopping medications if feeling worse. Regarding adherence to ART during the past week, 116 (76.8%) of patients reported never missing a dose, 30 (19.9%) reported missing 1-2 doses, 1 (0.6%) reported missing 3-5 doses, 2 (1.3%) reported missing 6-10 doses, and 2 (1.3%) reported

missing more than 10 doses. Concerning adherence to ART during the past 3 months, 128 (84.8%) reported missing 2 days or fewer of ART and 23 (15.2%) reported missing more than 2 days of medication.

Characteristics of Medications

Characteristics of medications are presented in Table 3. One hundred and fifty-one participants took 1,717 medications. For the purpose of the analysis, the term *medication* refers to any drug product including prescription drugs, OTC products, natural health products and dietary supplements. The most common drug class was antiretroviral (n=438, 25.5%); active antiretroviral use was an inclusion criterion for the study. The next most common drug classes were psychotropic (n=142, 8.3%); non-opioid analgesic (n=137, 8.0%); vitamin, mineral, electrolyte (n=132, 7.7%); anti-infective (n=123, 7.2%) and natural health product (n=80, 4.7%).

Table 3: Characteristics of medications (n=1717). *Medication* refers to any drug product that the patient takes, including prescription and non-prescription drugs.

Drug Class	Count (%)
Antiretroviral	438 (25.5)
Psychotropic	142 (8.3)
Non-steroidal anti-inflammatory and other non-opioid analgesic	137 (8.0)
Vitamin, mineral or electrolyte	132 (7.7)
Anti-infective	123 (7.2)
Natural health product	80 (4.7)
Cardiovascular	76 (4.4)
Endocrine (including hormones, contraceptives, anti-thyroid, anti-diabetic)	70 (4.1)
Inhaler or intranasal	61 (3.6)
Topical	59 (3.4)
Digestive	57 (3.3)
Cholesterol-lowering	56 (3.3)
Cold, allergy and sinus product	52 (3.0)
Acid-lowering	50 (2.9)
Other	46 (2.7)
Opioid analgesic	29 (1.7)
Blood medication (including anticoagulation, iron products)	29 (1.7)
Erectile dysfunction	22 (1.3)
Antiemetic	14 (0.8)
Anticonvulsant	12 (0.7)
Ophthalmic	12 (0.7)
Smoking cessation	7 (0.4)
Nitrate	7 (0.4)
Chemotherapy	5 (0.3)

Characteristics of Medication Errors

Characteristics of medication errors are presented in Table 4. Of 1,717 medications 1,144 (66.6%) were associated with at least one error. The overall frequency of medication errors was 1,699. A total of 995 (58.0%) medications had 1007 discrepancies between the patient's BPMH and the clinic's database list. A total of 435 medications had 447 discrepancies between the patient's BPMH and the community pharmacy list. Medication list comparisons revealed 645 (37.6%) medications were associated with

1001 omission errors, defined as medications that the patient was taking for which there was no documentation on the clinic database list or community pharmacy list. Drug classes that were most frequently associated with omission errors included non-opioid analgesics (n=110, 17.1%); vitamins, minerals and electrolytes (n=94, 14.6%), natural health products (n=69, 10.7%); cold, allergy and sinus products (n=43, 6.7%); topical products (n=41, 6.4%); and psychotropics (n=35, 5.4%). Forty-seven (2.7%) of medications were associated with 57 CSDI. Pharmacists identified 224 errors that reached patients, meaning that they had a severity rating of Category C or higher. Approximately 12% of medications had at least one error that reached the patient. Regarding errors that reached patients, 119 (6.9%) medications were associated with a total of 128 errors that required some form of intervention to preclude harm (i.e. Category D). Five medications (0.3%) were associated with errors that the pharmacists judged to have caused some kind of harm (i.e. Category E). The most frequently implicated drug classes associated with errors that reached patients included anti-infectives (n=37, 17.7%); antiretrovirals (n=29, 13.9%); psychotropics (n=29; 13.9%); non-opioid analgesics (n=13, 6.2%); inhalers and intranasal products (n=12, 5.7%); erectile dysfunction medications (n=12, 5.7%). Among 151 study patients, 147 (97.4%) had at least one medication error and 89 (58.9%) patients experienced at least one Category C error or higher.

Table 4: Characteristics of errors. Errors are presented as count (%) for a given medication and in terms of overall frequency, for the reason that one medication could be associated with multiple errors (n=1717).

Characteristic	**Count (%)**	**Overall Frequency**
Any error	1144 (66.6)	1699
Errors that reached patients (i.e. Category C or higher)	209 (12.2)	224
Database discrepancy	995 (58.0)	1007
Community pharmacy discrepancy	435 (25.3)	447
Error Types	**Count (%)**	**Overall Frequency**
Omission error	645 (37.6)	1001
Inappropriate dosing	215 (12.5)	238
Insertion error	180 (10.5)	186
Inappropriate frequency	139 (8.1)	156
Clinically significant drug interaction	47 (2.7)	55
Wrong drug	37 (2.2)	39
Therapeutic duplication	11 (0.6)	11
Inappropriate dosing for renal function	9 (0.5)	9
No indication	4 (0.2)	4
Error Severity	**Count (%)**	**Overall Frequency**
Category A	1049 (61.1)	1454
Category B	21 (1.2)	21
Category C	88 (5.1)	91
Category D	119 (6.9)	128
Category E	5 (0.3)	5

Stages in the Medication-Use System

The majority of medication errors occurred during the transcribing/documentation stage of the medication-use system (Table 5). Among 1,144 medications that were associated with at least one error, 994 (86.9%) had errors that were associated with clinic documentation and 418 (36.5%) had errors that were associated with the community pharmacy documentation. When considering only errors that reached patients, most errors were patient-related, occurring during the self-administration stage of the medication-use system (Table 6). Among 209 medications that were associated with Category C errors or higher, 149 (71.3%) had errors that were associated with the self-

administration stage and 64 (30.6%) had errors that were associated with the prescribing stage. Since one medication could be associated with more than one error and error severity category, the transcribing/documentation errors in Table 6 mainly represent discrepancy errors.

Table 5: Medication-use stages involved with errors (n=1,144). Data are presented as count (%) for a given medication and in terms of overall frequency, for the reason that one medication could be associated with multiple errors stages.

Medication-Use Stage	Count (%)	Overall Frequency
Prescribing	90 (7.9)	95
Transcribing/Documentation (Clinic)	994 (86.9)	1007
Transcribing/Documentation (Community Pharmacy)	418 (36.5)	429
Self-Administration	160 (14.0)	167

Table 6: Medication-use stages involved with errors of Category C severity or higher (n=209). Presented as count (%) for a given medication and in terms of overall frequency, for the reason that one medication could be associated with multiple errors stages.

Medication-Use Stage	Count (%)	Overall Frequency
Prescribing	64 (30.6)	68
Transcribing/Documentation (Clinic)	124 (59.3)	127
Transcribing/Documentation (Community Pharmacy)	30 (14.5)	34
Self-Administration	149 (71.3)	155

Number of Medication Errors and Patient Characteristics

Considering only errors that reached patients, a description of bivariate characteristics and the median (range) [IQR] number of errors per patient is presented in Table 7. This comparison revealed that males tended to have more errors than females (1 (0-9) [0-2] versus 0.5 (0-5) [0-1]); age 50 years or older tended to have more errors than age younger than 50 years (2 (0-9) [0-3] versus 0 (0-8) [0-2]); patients with suppressed viral loads tended to have more errors than those with uncontrolled viral loads (1 (0-9) [0-2] versus 0.5 (0-6) [0-1]); patients with five or more comorbidities tended to have more errors than patients with fewer than five comorbidities (2 (0-7) [0-3] versus 1 (0-9) [0-

2]); patients taking greater than ten medications tended to have more errors than those taking fewer than 10 medications (2 (0-9) [1-4] versus 0 (0-5) [0-1]); patients collecting prescriptions from more than one pharmacy tended to have more errors than patients collecting prescriptions from only one pharmacy (2 (0-7) [0-4] versus 1 (0-9) [0-2]). Patients who took investigational drugs tended to have fewer errors than patients who did not (0 (0-2) [0-1] versus 1 (0-9) [0-2]). Patients with a history of cardiovascular disease, diabetes mellitus, dyslipidemia or renal disease tended to have more errors than patients without these illnesses. Other patient characteristics that tended towards a higher number of errors included white race, being francophone, recreational drug use during the past month and missing three or more doses of ART during the past week. Patient characteristics that tended to have fewer errors included non-white and non-black race, being allophone, having refugee status and being born outside of Canada.

Table 7: Bivariate summary: median (range) [IQR] number of errors per patient, by demographic or clinical characteristic (n=151). Only errors that reached the patient are presented (i.e. Category C and higher).

Characteristic	Yes	No
Age ≥ 50 years	2 (0-9) [0-3]	0 (0-8) [0-2]
Male	1 (0-9) [0-2]	0.5 (0-5) [0-1]
Men who have sex with men risk factor	1 (0-8) [0-2]	1 (0-9) [0-1.5]
Heterosexual risk factor	1 (0-9) [0-2]	1 (0-8) [0-1]
Injection drug use risk factor	1 (0-4) [0-2]	1 (0-9) [0-2]
Endemic risk factor	1 (0-9) [0-1]	1 (0-8) [0-2]
Blood transfusion risk factor	3 (0-4) [1-4]	1 (0-9) [0-2]
Mother-to-child-transmission risk factor	0 (0-0) [0-0]	1 (0-9) [0-2]
Black race	0 (0-9) [0-1]	1 (0-8) [0-2]
White race	2 (0-8) [0-3]	0 (0-9) [0-1]
Other race	0 (0-2) [0-1]	1 (0-9) [0-3]
Anglophone	1 (0-9) [0-2]	1 (0-8) [0-2]
Francophone	1.5 (0-9) [0-3]	0 (0-9) [0-1]
Allophone	0 (0-8) [0-1]	1 (0-9) [0-3]
Born outside of Canada	0 (0-8) [0-1]	2 (0-9) [0-3]
Refugee status	0 (0-3) [0-1]	1 (0-9) [0-2]
High school education or greater	1 (0-9) [0-2]	1 (0-3) [0-1]
HIV-hepatitis C co-infection	1 (0-4) [0-2]	1 (0-9) [0-2]
Patient has ≥ 5 comorbidities	2 (0-7) [0-3]	1 (0-9) [0-2]
History of cardiovascular disease	2 (0-9) [1-4]	1 (0-7) [0-2]
History of diabetes mellitus	2.5 (0-5) [0.5-4]	1 (0-9) [0-2]
History of dyslipidemia	2 (0-8) [1-3]	1 (0-9) [0-2]
History of renal disease	2 (0-5) [1-3]	1 (0-9) [0-2]
Tobacco use during past year	1 (0-8) [0-2]	1 (0-9) [0-2]
Alcohol use during past year	1 (0-8) [0-2]	1 (0-9) [0-2]
Marijuana use during past year	1 (0-6) [1-2]	1 (0-9) [0-2]
Other recreational drug use during past month	2 (0-6) [1-3]	1 (0-9) [0-2]
Patient takes ≥ 10 medications	2 (0-9) [1-4]	0 (0-5) [0-1]
Hospitalized during past year	1 (0-9) [0-2]	1 (0-8) [0-2]
Visited > 1 physician during past year	1 (0-9) [0-2.5]	1 (0-8) [0-2]
Prescriptions from > 1 pharmacy during past year	2 (0-7) [0-4]	1 (0-9) [0-2]
Patient takes investigational drugs	0 (0-2) [0-1]	1 (0-9) [0-2]

Characteristic	Yes	No
Missed ≥ 3 doses of ART during past week	2 (0-7) [0-2]	1 (0-9) [0-2]
Missed ≥ 2 days of ART during past 3 months	1 (0-7) [0-3]	1 (0-9) [0-2]
HIV-RNA below 50 copies/mL	1 (0-9) [0-2]	0.5 (0-6) [0-1]
Glomerular filtration rate < 50 mL/min	1 (0-8) [1-2.5]	2 (0-9) [0-2]

Number of Medication Errors and Drug Classes

A description of drug classes taken by patients and the median (range) [IQR] number of errors (Category C or higher) per patient is presented in Table 8. This comparison revealed that the patients taking the following drug classes tended to have more errors: acid-lowering medications; antiemetics; cholesterol-lowering medications; cold, allergy, and sinus products; digestive medications; erectile dysfunction medications; inhalers and intranasal products; nitrates; non-opioid analgesics; opioid analgesics; psychotropics; smoking cessation medications; topical products; and vitamins, minerals and electrolytes.

Table 8: Bivariate summary: median (range) [IQR] number of errors per patient according to the drug classes taken by the patient (n=151). Only errors that reached the patient are presented (i.e. Category C and higher).

Patient medications by drug class	Yes	No
Acid-lowering	2 (0-9) [1-4]	1 (0-7) [0-1]
Anti-infective	1 (0-9) [0-3]	0 (0-7) [0-2]
Anticonvulsant	1 (0-5) [0-2]	1 (0-9) [0-2]
Antiemetic	1.5 (0-9) [0.5-4]	1 (0-8) [0-2]
Antiretroviral	1 (0-9) [0-2]	-
Blood medication	1 (0-9) [0-2]	1 (0-8) [0-2]
Cardiovascular	1 (0-8) [0.5-4]	1 (0-9) [0-2]
Chemotherapy	1 (0-9) [0-9]	1 (0-8) [0-2]
Cholesterol-lowering	2 (0-9) [1-4]	1 (0-7) [0-2]
Cold, allergy and sinus product	2 (0-9) [0-3]	1 (0-8) [0-2]
Digestive	2 (0-9) [1-4]	0 (0-7) [0-1]
Endocrine	1 (0-8) [0-2]	1 (0-9) [0-2]
Erectile dysfunction	2.5 (0-8) [1-4.5]	1 (0-9) [0-2]
Inhaler/intranasal	2 (0-9) [1-3]	1 (0-8) [0-2]
Natural health product	1 (0-9) [0-3]	1 (0-7) [0-2]
Nitrate	3 (0-5) [2-4]	1 (0-9) [0-2]
Non-opioid analgesic	1 (0-9) [0-2]	0 (0-7) [0-2]
Opioid analgesic	2 (0-8) [1-3]	1 (0-9) [0-2]
Ophthalmic	1 (0-7) [0-5]	1 (0-9) [0-2]
Psychotropic	2 (0-9) [1-3]	0 (0-6) [0-1]
Smoking cessation	2 (1-7) [1-3]	1 (0-9) [0-2]
Topical	2 (0-7) [1-3]	1 (0-9) [0-2]
Vitamin, mineral or electrolyte	1 (0-9) [0-3]	0.5 (0-7) [0-2]

Medication Error Severity

For analysis using a proportional odds model, each medication was classified into one of four categories of increasing severity (Table 9). Among 1,717 medications, 573 (33.4%) were associated with no error; 935 (54.5%) were associated with errors that did not reach the patient (i.e. Category A or B); 87 (5.1%) were associated with errors that reached the patient, but required no intervention (i.e. Category C); 122 (7.1%) were associated with

errors that reached the patient, required intervention, with or without causing patient harm (i.e. Category D or E).

Table 9: Medications classified by clinical severity of the error (n=1717).

Error Severity Category	Count (%)
No error	573 (33.4)
Error did not reach patient (A or B)	935 (54.5)
Error reached patient, no intervention (C)	87 (5.1)
Error reached patient, intervention, with or without causing harm (D or E)	122 (7.1)

Impact of Covariates on Number of Medication Errors

Clinical and demographic characteristics that were significantly associated with a higher number of errors (Category C or higher) in univariate analyses included the following: age, years since HIV diagnosis, number of comorbidities, number of concomitant medications, number of OTC products, history of cardiovascular disease, history of dyslipidemia, and missing 3 or more doses of ART during past week. Another potentially clinically interesting covariate was obtaining prescriptions from more than one pharmacy during past year. Clinical and demographic characteristics that were significantly associated with a lower number of medication errors in univariate analyses included race other than black or white race, being allophone, being born outside of Canada, and being refugee.

Medication classes that were significantly associated with a higher number of errors in univariate analyses included the following: anti-infectives; acid-lowering medications; cardiovascular medications; cholesterol-lowering medications; digestive medications; endocrine medications; erectile dysfunction medications; inhalers and intranasal products; natural health products; non-opioid analgesics; opioid analgesics; psychotropics; topical products; and vitamin, mineral and electrolytes.

Clinical and demographic characteristics that were not significantly associated with a higher number of errors in univariate analyses included the following: sex, HCV or HBV

coinfection, history of diabetes, history of renal disease, seeing another physician during the past year, being hospitalized during past year, level of education, history of IDU, tobacco use, alcohol use, marijuana use.

The final multivariate model for the number of medication errors (Table 10) included the following covariates: the number of concomitant medications, years since HIV diagnosis, allophone patients, anti-infectives, cardiovascular disease, erectile dysfunction medications, and poor adherence (i.e. patients who had missed $\geq$ 3 doses of ART during past week).

Impact of Covariates on Medication Error Severity

Clinical and demographic characteristics that were significantly associated with more severe errors in univariate analyses included the following: years since HIV diagnosis, number of concomitant medications, blood transfusion risk factor, obtaining prescriptions from more than one pharmacy during past year, number of OTC products, and having a high school education or higher. Allophone patients, refugee patients, and patients with a higher number of day hospital visits during past year were less likely to experience severe errors. Another potentially clinical interesting covariate included history of cardiovascular disease.

Medication classes that were significantly associated with more severe errors in univariate analyses included the following: anti-infectives; antiemetics; blood medications; chemotherapy; erectile dysfunction medications; digestive medications; inhalers or intranasal products; nitrates; natural health products; non-opioid analgesics; psychotropics; topical products; and vitamins, electrolytes and minerals.

Clinical and demographic characteristics that were not significantly associated with more severe errors in univariate analyses included the following: age, sex, number of comorbidities, having a suppressed HIV viral load, history of HCV or HBV coinfection, history of dyslipidemia, history of renal disease, GFR, seeing more than one physician during the past year, being hospitalized during the past year, interacting with an HIV

clinical pharmacist during the past year, history of IDU, tobacco use, alcohol use, marijuana use, and other recreational drug use during past month.

The final multivariate model for error severity (Table 11) included the following covariates: anti-infectives; chemotherapy; erectile dysfunction medications; inhalers and intranasal medications; natural health products; non-opioid analgesics; number of day hospital visits; number of over-the-counter products; prescriptions from > 1 pharmacy; psychotropics; vitamins; and years since HIV diagnosis.

Table 10: Number of errors per patient: results of univariate and multivariate analyses. Poisson model with robust standard errors including only errors that reached the patient (i.e. Category C and higher).

	Univariate Analysis				Multivariate Analysis			
Covariate	**Mean Multiplicative Change in Number of Errors**	**95% Confidence Interval**		**P Value**	**Mean Multiplicative Change in Number of Errors**	**95% Confidence Interval**		**P Value**
Age	1.0363	1.0183	1.0546	0.0001	-	-	-	-
Race other than black or white	0.3179	0.1566	0.6455	0.0018	-	-	-	-
Allophone	0.3343	0.1887	0.5924	<0.0001	0.4993	0.3206	0.7776	0.0025
Born outside Canada	0.4798	0.3044	0.7564	0.0019	-	-	-	-
Refugee status in Canada	0.2740	0.1077	0.6971	0.0073	-	-	-	-
Years since HIV diagnosis	1.0789	1.0365	4.8673	0.0420	1.0245	0.9978	1.0520	0.0694
Number of comorbidities	1.1213	1.0465	1.2014	0.0014	-	-	-	-
History of cardiovascular disease	2.0809	1.3851	3.1260	0.0006	1.4658	1.0449	2.0559	0.0284
History of dyslipidemia	1.8996	1.2758	2.8286	0.0019	-	-	-	-
Number of concomitant medications	1.1162	1.0906	1.1424	<0.0001	1.0764	1.0443	1.1090	<0.0001
Number of OTC products	1.1458	1.0652	1.2325	0.0004	-	-	-	-
Anti-infective use	1.9232	1.2762	2.9894	<0.0021	1.4144	1.0196	1.9621	0.0397
Acid-lowering medication use	2.8304	1.9729	2.8984	<0.0001	-	-	-	-
Cardiovascular medication use	1.7956	1.9729	4.0608	0.0051	-	-	-	-

	Univariate Analysis				Multivariate Analysis			
Covariate	**Mean Multiplicative Change in Number of Errors**	**95% Confidence Interval**		**P Value**	**Mean Multiplicative Change in Number of Errors**	**95% Confidence Interval**		**P Value**
Cholesterol-lowering medication use	2.6263	1.8079	3.815	<0.0001	-	-	-	-
Digestive medication use	2.7875	1.9331	4.0194	<0.0001	-	-	-	-
Endocrine medication use	2.0564	1.4075	3.0044	0.0003	-	-	-	-
Erectile dysfunction medication use	2.2885	1.4708	3.5609	0.0003	1.4068	0.9753	2.0292	0.0693
Inhaler or intranasal product use	1.7505	1.1509	2.6623	0.0098	-	-	-	-
Natural health product use	1.5618	1.0493	2.3245	0.0295	-	-	-	-
Non-opioid analgesic use	1.6958	1.0817	2.6587	0.0277	-	-	-	-
Opioid analgesic use	1.8112	1.1303	2.9022	0.0147	-	-	-	-
Psychotropic medication use	2.9463	1.8898	4.5935	<0.0001	-	-	-	-
Topical product use	1.5870	1.0172	2.4758	0.0436	-	-	-	-
Vitamin, mineral, electrolyte use	1.7890	1.1900	2.6895	0.0059	-	-	-	-
Prescriptions from > 1 pharmacy	1.6790	0.9658	2.9190	0.0683	-	-	-	-
Missed $\geq$ 3 doses ART during past week	2.2461	1.0523	1.106	0.0029	1.7816	0.9595	3.3075	0.0745

Table 11: Error severity: proportional odds model using robust standard errors. Results of univariate and multivariate analyses.

	Univariate Analysis				Multivariate Analysis			
		95% Confidence				95% Confidence		
Covariate	Odds ratio	Interval		P Value	Odds ratio	Interval		P Value
Blood transfusion risk factor	1.7161	1.0919	2.6970	0.0190	-	-	-	-
Allophone	0.7134	0.5358	0.9498	0.0210	-	-	-	-
Refugee status in Canada	0.6549	0.4592	0.9340	0.0190	-	-	-	-
High school education or greater	1.8481	1.2168	2.8068	0.0040	-	-	-	-
Years since HIV diagnosis	1.0215	1.0056	1.0377	0.0080	1.0172	1.0010	1.0337	0.0370
History of cardiovascular disease	1.3146	0.9609	1.7986	0.0870	-	-	-	-
Number of concomitant medications	1.0308	1.0088	1.0533	0.0060	-	-	-	-
Number of over-the-counter products	1.1016	1.0569	1.1483	<0.0001	1.0759	1.0191	1.1359	0.0080
Anti-infective use	2.4087	1.3612	4.2620	0.0030	4.5554	2.4209	8.5720	<0.0001
Antiemetic use	1.859	1.158	2.9845	0.0100	-	-	-	-
Blood medication use	2.2507	1.2016	4.2158	0.0110	-	-	-	-
Chemotherapy use	7.1992	1.6449	31.5082	0.0090	16.1715	4.0919	63.9113	<0.0001
Digestive medication use	2.0796	1.5682	2.7579	<0.0001	-	-	-	-
Erectile dysfunction medication use	9.3727	5.1947	16.9108	<0.0001	17.0918	8.7929	33.2233	<0.0001
Inhalers or intranasal medication use	3.0598	2.1233	4.4092	<0.0001	5.6300	3.6598	8.6609	<0.0001
Natural health product use	1.7664	1.3999	2.2289	<0.0001	2.6507	1.9587	3.5872	<0.0001
Nitrate use	2.8927	1.2688	6.5953	0.0120	-	-	-	-
Non-opioid analgesics	2.0837	1.6796	2.5851	<0.0001	3.3237	2.5271	4.3715	<0.0001

	Univariate Analysis				Multivariate Analysis			
		95% Confidence				95% Confidence		
Covariate	**Odds ratio**	**Interval**		**P Value**	**Odds ratio**	**Interval**		**P Value**
Psychotropic medication use	1.4895	1.0248	2.1650	0.0370	2.3995	1.5706	3.6659	<0.0001
Topical product use	2.0528	1.6038	2.6274	<0.0001	-	-	-	-
Vitamin, mineral, electrolyte use	1.5552	1.2129	1.9942	<0.0001	2.5051	1.7676	3.5503	<0.0001
Number of day hospital visits	0.9775	0.9633	0.9919	0.0020	0.9791	0.9634	0.9950	0.0100
Prescriptions from > 1 pharmacy	1.7416	1.0838	2.7986	0.0220	1.7574	1.0440	2.9582	0.0340

DISCUSSION

Pharmacists identified a high frequency (n=1,699) of medication errors in the study population, many which were of clinical relevance. Among 1,717 medications, the overall prevalence of errors that reached patients was 13%. Nearly 60% of patients experienced at least one medication error that had a Category C severity rating or higher.

Most errors (n=1454) were in the form of discrepancies between the clinic or community pharmacy medication lists and the BPMH. The most common drug-related problem detected was medication omission (n=1001). Non-prescription medications were most frequently associated with omission errors. Furthermore, our results demonstrate a widespread use of OTC products, natural health products and vitamins in study patients (n=125, 82.8%). The use of either natural health products or vitamins (n=86, 60.0%) was comparable to other studies of patients with HIV[97,99-104,106,107,109]. Although information on error rates of non-prescription medications is scarce, there is an increasing amount of literature describing adverse drug-drug and drug-disease interactions with OTC products[6].

With respect to errors that reached patients, the most common issues were incorrect dose, incorrect frequency and CSDI. Such errors occurred during the prescribing and the self-administration stages of the medication-use system. The most frequently implicated drug classes associated with errors that reached patients included anti-infectives, antiretrovirals, psychotropics, non-opioid analgesics, inhalers/intranasal products and erectile dysfunction medications. Errors that reached patients but did not require any intervention (i.e. Category C) generally involved instances when patients did not take medications according to the prescription label, but the pharmacists judged that the dose/schedule that they used was still clinically appropriate (e.g. prescription for lorazepam 1 mg HS, but patient takes lorazepam 0.5 mg HS prn and symptoms were managed at this dose and schedule). Examples of errors that reached patients and required intervention to preclude harm (i.e. Category D) included CSDI (e.g. inhaled fluticasone and ritonavir; atazanavir and tenofovir without ritonavir; nitroglycerin and tadalafil;

ritonavir and sildenafil 100 mg); inappropriate dose (e.g. tenofovir 300 mg DIE in a patient with a GFR< 50 mL; exceeding the maximum daily dose of pseudoephedrine); inappropriate frequency (e.g. Trizivir DIE versus BID; famciclovir 500 mg DIE for suppression therapy of herpes simplex virus disease); therapeutic duplication (e.g. taking two formulations of acetaminophen and exceeding the maximum daily dose); and patient omission error (e.g. self-discontinuation of lithium).

Regarding errors that were judged to cause some kind of harm and required intervention (i.e. Category E), the pharmacists identified a possible adverse drug reaction relating to the combination of etoposide and lopinavir/ritonavir. Upon the coadministration of these two drugs, the patient experienced a transaminitis (alanine aminotransferase and aspartate aminotransferase increased to 1174 IU/L and 424 IU/L, respectively). These symptoms subsequently improved when the drug combination was stopped and etoposide was restarted in the absence of lopinavir/ritonavir. Expert guidelines suggest that this adverse event is possible with this drug combination[129]. The Drug Interaction Probability Scale (DIPS)[135], an adapted version of the Naranjo Nomogram for Adverse Drug Reaction Assessment, was used to evaluate causation of this interaction. This case achieved a DIPS score of 4, suggesting possible causation. Another example of an error that was judged to have caused harm was in a patient receiving treatment for HCV and citalopram for depression. The patient mistakenly discontinued taking citalopram after one month of therapy and had uncontrolled depressive symptoms at the time of her study visit.

In the multivariate Poisson model (Table 10), the number of concomitant medications was associated with a higher number of medication errors that reached patients (mean multiplicative change in the number of errors 1.0764; 95% CI: 1.0443, 1.1090; $p<0.0001$). While the magnitude of the mean multiplicative change in the number of errors may seem small, this represents an increase in the mean multiplicative change of experiencing an error for every additional medication. Thus, this translates to a 7.6% increase in the number of errors per concomitant medication, or 44.5% increase in mean number of errors with five concomitant medications. This association is not surprising, and it reinforces the need for healthcare providers and patients to be vigilant when

managing lengthy medication lists and whenever a new medication is added to an existing regimen.

The association between years since HIV diagnosis and the number of medication errors was not statistically significant, but potentially clinically interesting (mean multiplicative change in the number of errors 1.0245; 95% CI: 0.9978, 1.0520; p=0.0694). For instance, the mean multiplicative change in the number of errors for a patient who was diagnosed with HIV 13 years ago (which was the median time of study patients) compared to a patient diagnosed with HIV 0 years ago is 37%. This association may be explained by the increasing complexity of medication regimens and comorbidities in patients with more advanced HIV disease.

Allophone patients, or those who spoke neither English nor French as a first language, were more likely to experience fewer errors than anglophone or francophone patients (mean multiplicative change 0.4993; 95% CI: 0.3206, 0.7776; p=0.0025). The reason for this association is not clear. It was suspected that the allophone population is representative of patients who were born outside of Canada and who tend to be younger (median=40.5 years; IQR: 37.0-45.0 versus median=49.0 years; IQR: 43.0-55.0) with fewer comorbidities (median=1; IQR: 1-3 versus median=4; IQR: 4-6). At the IDS, many of our refugees are younger and have HIV infection, but are otherwise healthy. However, when age and number of comorbidities were included in the multivariate model, the allophone coefficient remained stable. This finding does not support the idea that relative language barriers increase the risk of medication errors in this population. However, it is important to note that all patients who participated in the study had a reasonable level of English or French and no visits were carried out with the assistance of a translator.

Patients who took anti-infectives (mean multiplicative change 1.4144; 95% CI: 1.0196, 1.9621; p=0.0397) and erectile dysfunction medications (mean multiplicative change 1.4068; 95% CI: 0.9753, 2.0292; p=0.0693) had a greater risk of experiencing medication errors that were Category C or higher. These associations are logical, considering the CSDI and dosing issues that involved these classes. ARV medications were not included

as a covariate in the Poisson model because all patients took ART as an inclusion criterion of the study. In addition, patients with a history of cardiovascular disease were more likely to experience a higher number of errors (mean multiplicative change 1.4658; 95% CI: 1.0449, 2.0559; p=0.0284). This association is also reasonable when taking into account that medication regimens for patients with cardiovascular disease are typically complex and involve higher risk drugs. In a systematic review of preventable ADEs in ambulatory care patients, Thomsen *et al.* report cardiovascular medications as being the drug class most frequently associated with ADEs, preventable ADEs and preventable ADEs that required hospital admission[7]. Cardiovascular disease rather than cardiovascular medications was selected as a covariate in the final multivariate model in part because it had a much higher posterior probability (51.3% versus 11.9%) of being included in the best models according to the BIC and a stronger association in the multivariate model.

The results of this study also revealed that patients who reported missing three or more doses of ART during the past week might have a higher risk of experiencing more medication errors (mean multiplicative change 1.7816; 95% CI: 0.9595, 3.3075; p=0.0745). This association has low precision as demonstrated by the wide CI. Only 5 (3.3%) patients reported this level of poor adherence, which likely explains the CI width. In this study, suboptimal adherence to drug therapy was not considered to be a medication error unless it pertained to an incorrect dose, incorrect frequency, incorrect food requirements or the complete failure to take a prescribed medication. At best, we can reason the association between suboptimal adherence and medication errors is inconclusive based on these results.

In the multivariate proportional odds model (Table 11), medication errors were associated with a number of drug classes, including anti-infectives; chemotherapy; erectile dysfunction medications; inhalers and intranasal products; natural health products; non-opioid analgesics; psychotropic medications; and vitamins, minerals and electrolytes. These results are justifiable given that many of the medications in these drug classes are associated with clinically important drug interactions when combined with ARV drugs.

Using the error severity cut-points, the OR for having a Category A/B, C, D/E error versus no error is 4.56(95% CI: 2.42, 8.57) for medications that were anti-infectives versus medications that were not anti-infectives. One of the assumptions of the proportional odds model is that the ORs at specific cut-points are homogenous and thus, the summary OR is independent of the level of severity used to classify the outcome[134]. Therefore, another way to interpret the same OR of 4.56 is that it represents the summary ratio of the odds of having a more severe medication error, however one wishes to distinguish 'more' severe from 'less' severe. This is most likely why certain drug classes, such as vitamins and natural health products demonstrate large ORs despite being associated with less severe errors. These drugs classes were associated with many Category A omission errors. The ORs for several of the covariates presented in the multivariate model were relatively high; in particular, chemotherapy and erectile dysfunction medications had very large ORs and low precision (OR: 16.17; 95% CI: 4.09, 63.91 and OR: 17.09; 95% CI: 8.79, 33.22, respectively). These findings are most likely due to the small number of medications in each of these drug classes; of the 1,717 medications included in the analysis, only 5 (0.3%) accounted for chemotherapy and 22 (1.3%) were erectile dysfunction medications. Other medication classes, such as anti-infectives, inhalers/intranasal products, and psychotropics were linked to more severe errors and the direction of the associations presented in Table 11 seems reasonable notwithstanding the magnitude of the ORs. Of note, ARV medications were not included in the model because in univariate analysis, the coefficients showed a strong association for a decreased risk of medication error severity. We believe that this is a spurious association, given that active ARV use was an inclusion criterion of the study. The most reasonable explanation for this association is that many patients took only ART and were otherwise healthy, so it appears that ARV are association with a lower risk of medication errors.

Years since HIV diagnosis is also significantly associated with medication error severity (OR 1.02; 95% CI: 1.00, 1.03). Again, when considering a patient who was diagnosed with HIV 13 years ago compared to a patient diagnosed with HIV 0 years ago, the OR is 1.25, reflecting a higher odds of experiencing a medication error in patients with more

advanced disease versus patients with new HIV disease. These patients are likely to have acquired many more comorbidities may have more complex medication regimens.

A higher number of OTC products was significantly associated with medication errors (OR 1.08; 95% CI: 1.02, 1.14). This translates to an OR of 1.47 for patients who took 5 OTC products compared to patients who took none. OTC products were associated with many Category A omission errors which is the most likely reason for this association.

Patients who obtained prescription drugs from more than one pharmacy during the past year had a higher odds of experiencing a medication error than patients who obtained their prescriptions exclusively at one pharmacy (OR 1.76; 95% CI: 1.04, 2.96). This association has been documented in other studies[136,137]. In one retrospective study of 51,587 patients, Tamblyn *et al.*[136] found that patients who had a single dispensing pharmacy were less likely to have a potentially inappropriate drug combination than patients who went to more than one pharmacy. In another retrospective study, Kotzan *et al.*[137] describe a higher risk of receiving duplicate selective serotonin reuptake inhibitors (SSRIs) among patients who obtained prescriptions from multiple pharmacies. Using multiple pharmacies has also been reported to be associated with non-adherence and poor surveillance[138].

One potentially interesting finding was a modest association between the number of day hospital visits and a lower risk of severe medication errors (OR 0.98; 95% CI: 0.96, 0.99). The odds of a medication error in a patient who had 10 day hospital visits during the past year versus a patient who had no day hospital visits would be 0.81. One explanation for this association is that patients who have day hospital visits tend to be followed closely by the IDS team. Of note, one patient in the study population had 50 day hospital visits. When this patient was removed from the dataset and the results were re-analyzed, the effect of day hospital visits was no longer significant.

There were a number of clinical and demographic characteristics that were significantly associated with the frequency or severity of medication errors in univariate analyses,

which became non-significant in multivariate analyses. There could be several explanations for these findings, including issues around confounding. For instance, cholesterol-lowering medications were significantly associated with an increased number of medication errors in univariate analysis and in certain multivariate models despite the fact that very few (n=3) cholesterol-lowering drugs were actually associated with errors that reached patients. However, when cardiovascular disease was included in the model, cholesterol-lowering drugs was no longer significant, suggesting that there was a non-significant association that was confounded by cardiovascular disease in univariate analysis. Moreover, male sex was significantly associated with a higher number of errors in univariate and not multivariate analysis, but this association could have been confounded by other variables such as years since HIV diagnosis or cardiovascular disease. Fewer women than men participated in the study (n=28, 18.5%) and a high number of women refused to participate in the study (n=14, 45%), considering the proportion of women in the IDS population (0.28). There is a potential for selection bias although it is difficult to predict the direction of this bias. Suppose the men who chose to participate in the study were more responsible with their drug therapy than the men who chose not to participate. Suppose that the women who chose to not participate were vigilant with their healthcare, but too busy between work and home life to attend the study visits and no less responsible with their drug therapy than the women who partipcated. This bias could consequently create a spurious non-significant association between men and women and it is possible that gender is in fact a risk factor for experiencing a medication error. It is also possible that our sample simply lacked the power to detect an association with gender. The number of comorbidies did not show an increased risk of medication error frequency or severity in multivariate analyses. This may be because this covariate is correlated to the number of concomitant medications, which was included in the final Poisson model. This may also be because comorbidities were simply counted without considering the severity of the comorbid illness. For instance, a patient who reported having acne and seasonal allergies was considered to have two comorbidities, which was the same number for a patient who reported having congestive heart failure and non-Hodgkin's lymphoma.

Previous medication error studies involving outpatients with HIV are largely retrospective in nature; investigators used medical charts and prescription records as their main sources of data[12,17-19,29,30,33]. One other prevalence study involved patient interview, but the focus was outpatient IDU with HIV infection[34]. In the DEFEAT Study, patient-related medication errors were identified through comprehensive pharmacist-conducted interviews, which was a unique strength. In a randomized controlled study involving pharmacotherapy consultations in the general population, Jameson and VanNoord report that 73% of drug-related problems were discovered only during patient interview[81]. It is difficult to compare our findings to the results of other outpatient studies because of the differences in outcome definitions and methods of error detection. For instance, DeLorenze *et al.*[12] and Hellinger and Encinosa[17] identified risk factors associated with specific drug combinations. Willig *et al.*[30] investigated only NRTI dosing errors. It is equally difficult to compare the frequency and risk factors identified in the DEFEAT Study to the results of studies involving hospitalized patients with HIV. As patients transition from one level of care to another, they are at a notably high risk of experiencing medication errors[42]. We did not see an increased risk of medication errors with atazanavir as reported in other studies[9,24], although the restrictions for using atazanavir with acid-lowering drugs are much less conservative now than when these studies were published[117]. Moreover, we did not observe an increased risk of medication errors in patients who had compromised renal function as previously reported[8]. This may be because there were only 8 study patients who had GFR<50 mL/min. Depressive symptoms have been reported to be associated with medication errors in IDU outpatients with HIV[34]. We did not appreciate the same finding, although *history of any mental illness* was included in the statistical analyses rather than only *history of depression*. Likewise, the broader term *psychotropics use* was included in the analyses rather than *antidepressant use*. Pharmacists investigated all medication errors in the study population, rather than limiting the focus to ARV-related errors, which to our knowledge is different than any other published study on medication errors in outpatient PLHA.

Another strength of this study is that data collection included multiple sources (e.g. patient, pill bottles, pharmacy records, medical chart). Furthermore, two pharmacists

independently reviewed medication profiles and evaluated medication errors. Although we did not formally measure concordance, the agreement between pharmacist evaluations was high. In cases of discordance between evaluations, we did not have the resources to include a third pharmacist, but the pharmacists reached consensus. Only errors that reached patients were included in the Poisson model, in order to capture the most clinically relevant risk factors for medication error frequency. Lastly, aside from four missing heights, there were no missing data, as investigators made a solid effort to have complete information for the statistical analysis.

There are limitations to this study that are worthy of discussion. First, because of resources, the sample size was limited to 151 patients who took 1,717 medications. The relatively small sample size may explain the precision of our estimates, particularly in the proportional odds model. The majority of the patients interviews were conducted by two pharmacists who sought to standardize the structure of the interview, but it is possible that one pharmacist probed patients about medication use further than the other, creating a potential for interviewer bias. Patient recall, particularly regarding non-prescription medication use, may be another form of bias that influenced our results. Perhaps a characteristic such as older age affected a patient's ability to recall non-prescription drug use. In this case, fewer omission errors would be detected and the result could be a spurious non-significant association between age and medication errors. Furthermore, there was subjectivity in evaluating the severity of a medication error, and especially in judging whether harm occurred as a result of an error. There were very few medication errors that were judged to be associated with harm (n=5). In most of these cases, the patient experienced uncontrolled symptoms that were perceived to be as a result of taking the medication inappropriately or failing to take the medication. According to the NCC MERP definition, a Category E error considers errors that "may have contributed to or resulted in temporary harm…"[36]. As mentioned earlier, we used the DIPS to measure the likelihood of an adverse event caused by a CSDI between etoposide and lopinavir/ritonavir. In addition, this study was limited to a single ambulatory HIV clinic, although patients from other HIV clinics may experience similar types of errors. Lastly, the study population consisted of patients who were generally healthy and not

transitioning between levels of care, which means that our estimates of medication error frequency and severity are likely to be conservative.

Prevention and mitigation strategies at the IDS should target the prescribing, transcribing/documentation and self-administration stages of the medication-use system. There is a need to improve the documentation of a patient's prescription and non-prescription medications. One systems-based approach to obtaining the BPMH when a patient presents for a routine clinic visit would be to print a patient-friendly copy of the patient's medication history as documented in the clinic's database. The list could include a section for OTC and natural health products. The patient could review this list in the waiting room and note any changes to the physician, nurse or pharmacist. Subsequently, the data entry clerk could update the database medication list to reflect these changes. Another institution-wide strategy would be to implement a computerized physician order entry (CPOE) system through which clinic physicians could prescribe medications electronically. Ideally, CPOE would be integrated with a CDS system that could assist physicians with mediation management at the point of care. Examples of potential benefits of CPOE with CDS include alerts at the prescribing stage for drug-disease and drug-drug interactions, enhanced methods for prescription renewals and improved medication documentation. CPOE systems have the potential to reduce the incidence of mediation errors, improve health outcomes and lower medication-related costs[139,140]. Lastly, Quebec pharmacists with specialty training in HIV could provide didactic programs to community pharmacists and non-HIV specialists through *le Programme National de Mentorat sur le VIH/SIDA*. This mentorship program holds an annual symposium to educate community pharmacists about HIV pharmacotherapy. The findings of the DEFEAT Study could be shared during this conference with an emphasis on the most commonly observed errors. Strategies to improve the documentation of medication histories, and particularly non-prescription drugs, would also be a useful discussion.

Clinical pharmacists can a play a key role in identifying drug-related problems that occur during prescribing and self-administration. At the IDS, pharmacists offer a variety of

services to patients, including but not limited to counselling, adherence support, drug acquisition, drug information, drug interaction management, therapeutic drug monitoring, and medication reconciliation. The latter task is a demanding exercise, and to carry this out for each and every IDS clinic patient during routine medical follow-up would require at least two full-time pharmacists. One of the goals of the DEFEAT Study was to identify risk factors for medication errors, which could help HIV pharmacists to prioritize their clinical service. The results of two multivariate regression models suggest that certain drug classes, such as chemotherapy; erectile dysfunction medications; inhaler and intranasal drugs; and anti-infectives are associated with a higher frequency and/or severity of experiencing a medication error. Furthermore, a history of cardiovascular disease, a higher number of concomitant medications and a greater number of years since HIV diagnosis are also associated with a higher frequency and/or severity of experiencing a medication error. One proposal for a systems-based intervention would be to implement an alert function in the clinic database for patients with high-risk profiles for medication errors. These alerts would link to the clinic appointments for a given day so that pharmacists could opt to meet with patients who had a high potential for drug-related problems. Targeting higher risk patients is a reasonable starting point. An assessment of additional pharmacist workload and staffing costs of such a task is yet to be determined and could be a focus of future clinical research.

CONCLUSION

In this sample of ambulatory patients with HIV, pharmacists identified a high number of medication errors that reached patients and required intervention. Many of these errors were patient-related. Among errors that reached patients, the most common issues were incorrect dose, incorrect frequency and clinically significant drug interactions. To our knowledge, this was the first medication error study in an HIV ambulatory care setting that involved comprehensive pharmacist-conducted interviews. Possible risk factors for medication errors include certain drug classes, such as chemotherapy, erectile dysfunction drugs, inhalers and anti-infectives; the number of concomitant medications; the number of over-the-counter products; years since diagnosis; history of cardiovascular disease; and obtaining prescriptions from more than one pharmacy. Clinical pharmacists can be beneficial in identifying drug-related problems. Further research will focus on developing systems-based interventions such as alert functions that may assist pharmacists in better servicing clinic patients, reducing the numbers of errors and their potential harms to patients and minimizing costs to the healthcare system.

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