The impact of medication therapy management on polypharmacy in people living with HIV/AIDS

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BY

Helen Tolulope Orimoloye

Major Professor: Dr. Sumihiro Suzuki

Dr. Patrick Clay

Dr. Rafia Rasu

University of North Texas Health Science Center | School of Public Health

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ABSTRACT

Polypharmacy, defined as the concurrent use of multiple medications simultaneously, is increasingly common in people living with HIV/AIDS (PLWHA) due to the use of antiretroviral and non-antiretroviral drugs for the treatment of multiple chronic diseases. Polypharmacy is a growing concern among PLWHA because of their complex medication regimen, the risk of adverse drug events, drug-drug interactions, medication non-adherence, medication errors, and antiretroviral treatment failure.

Medication therapy management (MTM), which are pharmacist-led interventions, have been useful in resolving medication-related problems and optimizing clinical outcomes. However, there are limited studies on the effectiveness of pharmacist-provided MTM services in reducing polypharmacy in HIV/AIDs patients. MTM services should enable the identification and reduction of polypharmacy. Hence, the central goal of this dissertation was to evaluate the impact of MTM services on polypharmacy in PLWHA.

A secondary data analysis of a new MTM project by the CDC, UNTHSC, and Walgreens that involved the collaboration of pharmacists and clinicians to provide patient-centered care for HIV patients was done. The study involved 765 participants from 10 states in the United States. Polypharmacy was measured by the number of polyactive substances (pharmacologically active ingredients) in medications used. A paired T-test was used to find the difference between the pill count and the polyactive substances in medicines used by PLWHA. A longitudinal data analysis using a generalized estimating equation was used to assess the impact of MTM intervention on polypharmacy over time by determining the change in polyactive substances in medication pre-post MTM intervention. The relationship between the changes in HIV outcomes CD4 count and HIV RNA count and the change in polyactive substances pre-post MTM intervention was also determined.

The results showed a significant average difference between the polyactive substance count and the pill count of about 2.15. Also, the number of polyactive substances in medications used by study participants reduced by an average of 3 from pre- to post- MTM intervention. There was a relationship between the change in HIV outcomes and the change in polyactive substance pre-post MTM intervention. As polyactive substances decrease over time in the study, there is a higher chance that there is viral suppression and improvement in CD4 count at the end of the study.

Medication therapy management involving pharmacists and clinicians may be useful in addressing polypharmacy in PLWHA. The MTM program in this study was not designed to address polypharmacy. But the results indicated that the intervention had a positive impact on polypharmacy. Further studies, such as a case-control study or a randomized control trial, are required to assess the effect of MTM on polypharmacy better.

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CHAPTER 1: INTRODUCTION

1.1 Background

Due to the effective treatment of Human Immunodeficiency Virus (HIV) with the advent of antiretroviral therapy (ART), persons living with HIV/AIDS now have a life expectancy approaching that of the general population (Edelman et al., 2013). However, people living with HIV/AIDS are also having an increased risk of age-related comorbidities (Edelman et al., 2013; Krentz & Gill, 2016) with prevalent chronic diseases that may require the use of multiple medications throughout their life (Brown et al., 2005; Crothers et al., 2011; Freiberg et al., 2013). Studies have shown an increase in the prevalence of 2 or more chronic conditions in people living with HIV/AIDS. A study of adults with HIV in the US 22,969 adults with HIV in the United States (US) showed an increase in the prevalence of having multiple chronic diseases from 8.2% in 2000 to 22.4% in 2009 (Wong et al., 2018). Another study of adults with HIV in the US from different insurance payers: 36298 from commercial payers, 26246 from Medicaid, 1854 from Medicare providers between 2003 to 2013 reported the prevalence of hypertension to be (31.4%, 39.3% and 76.2%) and diabetes to be (11%, 17.8% and 37%) respectively (Gallant, Hsue, Shreay, & Meyer, 2017). Therefore, in addition to using multiple antiretroviral drugs, having chronic diseases has necessitated the increased use of multiple medications simultaneously (polypharmacy) in people living with HIV/AIDS (PLWHA). Different studies showed that on average, PLWHA take approximately 13 medications concurrently (Clay, 2004; Edelman et al., 2013; Greene, Steinman, McNicholl, & Valcour, 2014; Ware et al., 2018).

The use of ART in PLWHA is lifelong, and it promotes improvement in health outcomes and longevity (Krentz & Gill, 2016). However, medication use in people with HIV is increasingly complex due to the use of multiple antiretroviral and non-antiretroviral drugs (Krentz & Gill, 2016; Wong et al.,

2018). The increased use of medications in people with HIV/AIDs makes them a target population at risk for the dangers associated with polypharmacy.

Polypharmacy is defined as the concomitant use of multiple medications daily (Guthrie, Makubate, Hernandez-Santiago, & Dreischulte, 2015). Although the term polypharmacy has been widely used in the literature, there is no consensus on the number of medications for defining polypharmacy. While some studies have defined polypharmacy as the use of two or more medications concurrently (Brager & Sloand, 2005; Bushardt, Massey, Simpson, Ariail, & Simpson, 2008), a majority of researchers consider the use of five or more medications daily as a benchmark for describing polypharmacy (Greene et al., 2014). Some researchers have also described the use of between 6 to 9 medications as polypharmacy while considering the use of 10 or more drugs concurrently as excessive polypharmacy (Bushardt et al., 2008; Gnjidic et al., 2012; Guthrie et al., 2015). Nonetheless, using an arbitrary cutoff point to define levels of polypharmacy gives the impression that treatment for all diseases shouldn't exceed a maximum number of medications. This assumption is not true especially for chronic diseases like HIV/AIDS.

Due to the arbitrariness of cutoff points for defining polypharmacy, there is a current debate on whether to use the number of pills taken daily by an individual or the number of polyactive substances (pharmacologically active ingredients in medications) to measure polypharmacy (N. Abolhassani & Marques-Vidal, 2018; Castioni, Marques-Vidal, Abolhassani, Vollenweider, & Waeber, 2017; Rankin et al., 2018). Some authors think that with the advent of the "polypill," many drugs are combined into a single pill, thereby underestimating the prevalence of polypharmacy (N. Abolhassani & Marques-Vidal, 2018). Given that people with HIV have a complex antiretroviral medication regimen, some of their antiretroviral drugs have been compounded into a single pill to ease the pill burden. Knowing the substances in each medicine allows health care providers to identify the specific risk of each drug component correctly and is critical for predicting the extent to which any drug combination increases the

risk of adverse drug reactions (J. Aronson, 2004). Using the number of polyactive substances in medications to estimate polypharmacy is, therefore, essential for better risk assessment and management of the complex medication regimen in people living with HIV.

1.2 Public Health Significance

Polypharmacy is a growing public health problem that needs to be addressed through a concerted effort in research, education, clinical practice, and public policy (Nisly, Gryzlak, Zimmerman, & Wallace, 2010). Studies on a nationally representative sample of the general population showed that polypharmacy is increasingly common in the United States. About 10% of the entire population (Gu, Dillon, & Burt, 2010) and 37% of older adults (60 years or older) are taking five or more drugs concurrently (Gu et al., 2010; Sutherland et al., 2015). Another study using data from a nationally-representative sample showed that there is an increasing trend in the prevalence of polypharmacy in the US over time (8.2% in 2009 to 15% in 2012) (Kantor, Rehm, Haas, Chan, & Giovannucci, 2015). Similarly, other countries like the United Kingdom (Guthrie et al., 2011; Payne, 2016), China (Dong, Yan, & Wang, 2010), Sweden (Hovstadius, Hovstadius, Åstrand, & Petersson, 2010), and Brazil (Oliveira, Amorim, de Jesus, Rodrigues, & Passos, 2012) have reported a high prevalence of polypharmacy, making it a global health issue.

Polypharmacy can result in the excessive and inappropriate use of medications with the increased likelihood of adverse drug events, the risk of drug interactions, increased chances of medication errors, and increased financial burden to the patient (Payne & Avery, 2011). A prospective study on a cohort of 9,473 HIV positive and 39,812 HIV negative individuals examined the association between polypharmacy and hospitalization. The study showed that polypharmacy was associated with a 47% increased risk of hospitalization in those with HIV when compared to those without HIV, and that there

was a dose-response relationship between the number of drugs and the risk of hospitalization. The study showed that for each additional non-HIV drug, the risk of hospitalization increases by 8% (Justice et al., 2018). When the risks associated with polypharmacy are combined, it increases the risk of hospitalizations and readmissions far more than the risk conferred by comorbidities alone—thus making it a significant concern for health care systems.

Polypharmacy increases the risk of drug-related morbidity, with adverse drug reactions being one of the significant consequences (Rambhade, Chakarborty, Shrivastava, Patil, & Rambhade, 2012; Shehab et al., 2016). In the US, adverse drug reactions cause about four hospitalizations per one thousand people per year (Shehab et al., 2016), and it is one of the top ten causes of death (Makary & Daniel, 2016). The estimated annual cost associated with the treatment of adverse drug reactions ranges from 30 to 180 billion dollars (Ernst & Grizzle, 2001; Sultana, Cutroneo, & Trifirò, 2013). Other risks associated with polypharmacy include drug duplication, potentially inappropriate medications, drug-drug interactions, increased side effects, increased pill burden, organ-system injury, hospitalizations, and medication nonadherence (Duerden, Avery, & Payne, 2013). A study on a sample of 38,250 Medicare beneficiary adults, showed that 47.2% of them have polypharmacy, and 56.6% of them have potentially inappropriate medicines (Jirón et al., 2016). Potentially inappropriate medicines have been associated with adverse effects on long-term physical and cognitive functioning. In recognition of the potential harms of polypharmacy, regular monitoring, and review of medications at the patient level may create opportunities to deprescribe medications that are unnecessary or inappropriate. Deprescribing medications is defined "is the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes" (Thompson & Farrell, 2013).

Multiple comorbidities is a well-known cause of polypharmacy, but the increasing prevalence of polypharmacy can also be attributed to clinical practices that enable drug over-prescription and insufficient monitoring (Duerden et al., 2013). With HIV patients older than 50 years now accounting for

over half of all PLWHA in the developed world (Krentz & Gill, 2016) and having multiple chronic comorbidities, they are more likely to have increased polypharmacy. Studies on people with HIV estimate the prevalence of polypharmacy (use of 5 pills or more) to range between 23% to 42% (Guaraldi et al., 2018; Justice et al., 2018; Okoli et al., 2020; Siefried et al., 2018). These studies give an insight into the prevalence of polypharmacy in PLWHA.

The use of multiple medications concurrently in HIV infected adults increases the risk of pharmacokinetic interactions. Also, the use of HIV and non-HIV drugs can result in synergistic, additive, or antagonistic effects of the medications (Siefried et al., 2018). Studies have found contraindicated combinations of ART and other non-HIV drugs in 2% to 7% of HIV patients on treatment (Holtzman et al., 2013; Marzolini et al., 2010).

The use of ART may itself constitute polypharmacy as some HIV patients use between three to five antiretroviral drugs (Edelman et al., 2013; Krentz & Gill, 2016). The use of ART, coupled with the use of other non-antiretroviral medicines, further increases polypharmacy in PLWHA. As mentioned, polypharmacy increases the pill burden, which may lead to medication nonadherence. Nonadherence to ART is a critical concern in PLWHA because it may result in compromised HIV care or treatment failure (Krentz & Gill, 2016). Regular medication monitoring and reconciliation are needed in PLWHA to address medication-related issues, achieve optimal therapeutic outcomes, and complete viral suppression.

Balancing the risks and benefits of a medication regimen is particularly challenging for the health care providers of PLWHA. Many HIV patients have a complex medication regimen

due to the presence of increased age-related comorbidities such as cardiovascular disease (Freiberg et al., 2013), chronic pulmonary disease (Crothers et al., 2011), osteoporosis (Brown & Qaqish, 2006), and cognitive impairment (Heaton et al., 2011; Valcour et al., 2004). These diseases require treatment with multiple drugs often used concurrently (polypharmacy). Undesirably, using multiple medications concurrently increase the risk of potential drug-disease interactions, decreased metabolism, and clearance

of drugs as well as impaired storage of medications in the body (Salazar, Poon, & Nair, 2007). These metabolic changes with medication use are more detrimental to the aging HIV population.

The risks associated with polypharmacy in PLWHA may appear similar to the risk in the general population. However, people with HIV are more susceptible to the harm from polypharmacy (Edelman et al., 2013) because they have decreased organ system reserve, chronic inflammation, and ongoing immune dysfunction (Deeks, 2011; Justice, 2010). Also, most of them have liver and renal diseases which impairs drug metabolism and excretion (Joshi, O'Grady, Dieterich, Gazzard, & Agarwal, 2011; Medapalli et al., 2012) resulting in increased prevalence of drug-drug interactions and drug-related toxicity. Drug-drug interactions may go unnoticed in PLWHA due to the use of many drugs. A cohort study of 159 HIV patients reported clinically significant drug-drug interactions in 27% of the study population, and only 35% of these interactions were identified correctly by clinicians (Evans-Jones et al., 2010). Frequent drug interactions increase the risk of drug toxicity and treatment failure among PLWHA which may necessitate frequent changes in ART regimen (Edelman et al., 2013).

ART regimen consists of a combination of two nucleoside reverse transcriptase inhibitors (NRTI) administered with a third active antiretroviral drug from one of the three drug classes: either an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) with a pharmacokinetic enhancer (NIH, 2019). These drugs are combined in varying forms to constitute highly active antiretroviral therapy (HAART). HAART is effective in reducing viral load and preventing the development of AIDS. Since the introduction of HAART, AIDS-related events and deaths have decreased in clinical settings. However, HAART has the potential for toxicity, and a lack of adherence predispose to treatment failure. A study on 1189 HIV naïve patients who discontinued first-line HAART within the first year of therapy evaluated the reasons for change in therapy. The results showed that 58.5% of the population discontinued first-line therapy due to drug toxicity (Cicconi et al., 2010). A similar study on 1866 HIV patients compared the incidence, reasons and predictors of treatment change

within 1 year of starting combination HIV therapy between 2001 and 2005. 7.1% of those of who changed their regimen within a year was due to treatment failure (Vo et al., 2008). The known causes of antiretroviral treatment failure include poor adherence, drug resistance, inadequate dosing, and drug-drug interactions (Monforte et al., 2000; NIH, 2019).

The continued use of an ART regimen when there is treatment failure may result in mutations and the development of drug resistance (Babiker, 2011). Therefore, treatment failure requires frequent changes in ART regimen. However, the available anti-HIV drug classes are limited. Once there is treatment failure, those specific drugs can no longer be used (i.e., they are now inactive against the virus). The choices available for a new ART regimen will be limited (Krentz & Gill, 2016). Therefore, remaining on a single type of ART regimen that successfully suppresses viral replication is essential for slowing the progression of HIV and preserving options for future treatment. As such, it is necessary to understand the complex factors that impact treatment and medication adherence in this population.

1.3 Addressing polypharmacy in PLWHA

Complex medication regimens are particularly challenging to manage because of multiple daily doses and special administration instructions and may be potentially harmful if misused. It has been shown that increased prescription of multiple medications may not be enough for improving the quality of life or health outcomes (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008). Therefore, PLWHA with polypharmacy require regular medication review and optimization to ensure medication safety. There is, however, not much evidence in the literature on attempts to reduce polypharmacy in PLWHA. One successful strategy that may be effective in reducing the number of inappropriate drugs taken by HIV patients in the community may involve pharmacists reviewing the patients' medication lists and then discussing recommended changes with the prescribing doctor.

Pharmacist-led interventions such as medication therapy management (MTM) have been useful in resolving medication-related problems and optimizing clinical outcomes. Studies in HIV patients have shown that MTM has the benefits of improving medication adherence, reducing contraindicated therapy, remaining on a single type of ART regimen, and preventing excess medication refills for ART(Cantwell-McNelis & James, 2002; Hirsch et al., 2011; Hirsch, Rosenquist, Best, Miller, & Gilmer, 2009; March, Mak, & Louie, 2007). These studies only focused on ART and did not include other medicines used by PLWHA that may contribute to polypharmacy. From the review of literature, the effectiveness of pharmacist-provided MTM services in reducing polypharmacy in HIV/AIDs patients has not been well studied. It is expected that MTM services should enable the identification and reduction of polypharmacy. Hence, the central goal of this dissertation is to evaluate the impact of MTM services on polypharmacy in PLWHA.

A study on a cohort of PLWHA in Ontario examined the impact of polypharmacy (number of drugs used at the beginning of the study and the number of drug classes used) on antiretroviral (ARV) regimen and formulations. The goal was to determine if there was a relationship between polypharmacy and the rate of discontinuing or switching ART (Krentz & Gill, 2016). The authors of the study found an association between polypharmacy and non-continuous ART regimen, age, lower CD4 count, AIDS diagnosis, and living with HIV for more than 15 years and using four or more ARV regimen. The study by Krentz et al. examined the number of drugs used at the beginning of the study as determined from the patient records but did not observe how the medication regimen changed over time. Knowing how medication changes over time is important in monitoring the risks associated with polypharmacy and assessing the impact of health interventions such as MTM on polypharmacy. To effectively reduce the associated risks of polypharmacy, it is essential to identify and accurately measure the actual prevalence of polypharmacy during interventions to address medication safety.

The first step in addressing polypharmacy in people with HIV/AIDS is to be able to measure polypharmacy and determine its prevalence accurately. Existing evidence demonstrates that there is no consensus in the literature on the cut off points and methods of measuring polypharmacy. Most researchers have used five pills or more as a benchmark for defining polypharmacy. Using five or more pills to define polypharmacy in people with HIV may be too naïve because this population takes more medications when compared to other chronic diseases.

Therefore, the cut off for defining polypharmacy should be population-specific.

Similarly, while the use of 5 pills has been a useful approach, there may be some considerable limitations. Given that with the advent of drugs like the "polypill" (N. Abolhassani & Marques-Vidal, 2018; Castioni et al., 2017), multiple pharmacologically active substances (polyactive substances) are now being combined into one pill as a fixed-dose combination. For example, there are currently 22 single-pill combinations of HIV drugs: Imduo, Combivir, Descovy, Epzicom, Temixys, Trizivir, Truvada, Atripla, Complera, Delstrigo, Odefsey, Symfi, Biktarvy, Dovato, Triumeq, Juluca, Genvoya, Stribild, Symtuza, Evotaz, Prezcobix, and Kaletra (NIH, 2019). Each of these drugs contains about two to three antiretroviral agents combined into one pill. Atripla is a combination of efavirenz, emtricitabine, and tenofovir. Therefore, a patient taking Atripla is taking one pill but three polyactive substances. People may experience more side effects when these fixed-dose combination drugs are used with other non-antiretroviral drugs. However, it may be hard to determine which active substance is causing an adverse effect. It is, therefore, necessary to accurately measure polypharmacy using polyactive substances. For this dissertation, polyactive substances are defined as the total number of pharmacologically active ingredients in medications used by an individual.

Some researchers have argued that not considering the number of polyactive substances in medications when defining polypharmacy may lead to an underestimation of the true prevalence of polypharmacy (N. Abolhassani & Marques-Vidal, 2018; Castioni et al., 2017). For example, a study by

Abolhassani et al. showed the differences in the measure of polypharmacy when using the number of pills as against using the number of polyactive substances. The authors showed that the prevalence of polypharmacy (defined by the number of pills) was 11.9%. However, when the number of polyactive substance was used as a measure, the prevalence of polypharmacy increased to18% in the same study population (N. Abolhassani & Marques-Vidal, 2018). Knowing the number of polyactive substances in medications is essential because the risk of drug-drug interaction increases exponentially with each additional medicine used (Hovstadius et al., 2010). The exact risk of adverse events that occurs with polypharmacy can be predicted more accurately when the number of polyactive substance in medications measures polypharmacy. However, the difference between pills and polyactive substances is not clear in the literature on HIV as there have been no studies in PLWHA that use the number of polyactive substance to define polypharmacy.

Considering the risks associated with polypharmacy, regular medication monitoring, and review through medication therapy management (MTM) is needed to optimize clinical outcomes in people with HIV. MTM services are pharmacist-driven interventions that address or resolve medication-related problems and improve clinical outcomes (Byrd, Hardnett, et al., 2019). The first step in an MTM service is the medication therapy review, which is a systematic process of assessing medication regimens for indication, safety, effectiveness, and adherence. Medication therapy review may include the review of the response to therapy and appropriateness of each medication (e.g., proper dosing, clinical indications) (Byrd, Hardnett, et al., 2019). Pharmacists can detect polypharmacy and determine if it is appropriate or not during medication therapy review. Collaborative care provided by community pharmacists and primary care physicians has the potential to further improve medication use by allowing strategies to deprescribe medications when they are no longer needed, when they cause side effects or are inappropriate.

As one of the efforts to improve retention in HIV care, adherence to ART, and viral suppression among PLWHA, the Centers for Disease Control (CDC) in a novel public-private partnership with Walgreens Pharmacy funded the University of North Texas Health Science Center to implement the Patient-centered HIV Care Model (PCHCM). The goal of the PCHCM model was to provide patient-centered care for people with HIV by integrating the services of community-based HIV trained pharmacists with primary medical providers. The PCHCM model builds on the Medication Therapy Management (MTM) model by making the primary care providers to share the clinical information of patients with their partnered pharmacists to enable the pharmacists to conduct MTM precisely. The pharmacists then conduct an initial comprehensive medication review (CMR) by assessing the medication regimen for indication, safety, effectiveness, and adherence. The pharmacist met with the patients to provide individualized care, educate the patients to improve their understanding of the treatment plan and the appropriate use of medications. The pharmacists also assess the patients for drug interaction and response to therapy and prescription filling patterns. It is believed that this intervention among HIV patients would have a positive impact on adherence to medication and reduce polypharmacy.

Studies have shown that pharmacist intervention in the management of patients through comprehensive medication review can help with identifying problems with medications (Byrd, Hou, et al., 2019; March et al., 2007). Pharmacists have been able to detect patients access to previously prescribed medications, over the counter (OTC) medications, alternative drugs and drug-drug interactions (Izzo & Ernst, 2009; Mallet, Spinewine, & Huang, 2007; Stolbach, Paziana, Heverling, & Pham, 2015). Such programs have helped to reduce polypharmacy by identifying patients who are on duplicate medications. A typical example of duplicate medication use are those receiving nonsteroidal anti-inflammatory drugs from both prescription and over the counter sources (Rambhade et al., 2012). One of the objectives of this study is to determine if medication therapy management had any impact on the quantity of the polyactive substances in medications used by people living with HIV/AIDS.

Medication reconciliation is one of the most effective measures for decreasing adverse drug events and improving patient care with regards to therapeutic safety (Calderón-Larrañaga et al., 2012). In this study, the PCHCM program performed the task of conducting a pharmacological review of the patient and removing medications that are redundant, contraindicated, or not indicated. This program is the first of its kind to undertake comprehensive medication management in PLWHA. It is therefore desirable to examine how this program improved medication management in this group and the effect on HIV-related outcomes.

In this study, we propose to use the data from the PCHCM program to determine if the program had any effect on the number of polyactive substances in the medications of the participants. Similarly, we will be able to identify other factors that contributed to the increase or decrease in the quantity of the polyactive substance in medications used by participants in this study. We hope to determine if the change in the quantity of polyactive substances in the medication regimen affects disease outcomes in PLWHA.

Implications

This study used the number of polyactive substances in the medication regimen rather than the pill count to estimate polypharmacy in people living with HIV/AIDS. This approach will help to emphasize the prevalence of polypharmacy in PLWHA better. If the community-based pharmacist intervention done in this study is proven to improve polypharmacy and health outcomes in PLWHA, the research findings will inform the expansion of the program and increase its acceptability. It will show the impact of a strategy that reviews the health problems of PLWHA in totality rather than for a specific illness. This knowledge will be useful in developing solutions to address the problems that are associated with the use of multiple medications. This study will also show if medication interventions by trained pharmacists improve HIV-related and overall health outcomes in PLWHA.

Gaining a more in-depth understanding of the findings in this study will help to determine the effect of PCHCM on polypharmacy. It will help to promote scientific advancement for HIV management and further help to identify the barriers that may have to be addressed in interventions to improve HIV antiretroviral treatment adherence. In light of these gaps, this dissertation will be guided by the aims below.

1.4 Specific Aims

The specific aims of this study are:

Aim 1: Determine the difference between the pill count and the number of polyactive substances in medicines of PLWHA population enrolled into a patient-centered HIV care model demonstration project.

Aim 2: Determine the relationship between polypharmacy as defined by the number of polyactive substances in medications used by PLWHA at the beginning and at the end of a modified MTM intervention program and the factors that may affect the change in the number of polyactive substances.

Aim 3: Examine the relationship between the number of polyactive substances and the changes in HIV-related outcomes such as CD4 count and viral load suppression during a modified MTM intervention program.

Upon completion of these aims, the expected outcomes are to have demonstrated that the use of the number of polyactive substances in medicines may be a more accurate indication of polypharmacy than the use of pill count. We expect that MTM programs are useful in reducing polypharmacy. Furthermore, we expect that a reduction in polypharmacy will be associated with an improvement in HIV-related outcomes.

In the following chapter, the literature review will focus on the disease in the subject of interests (HIV/AIDS), describing their drug use and the factors that determine their drug use pattern. It will also focus on the outcome variable (Polypharmacy used interchangeably with polyactive substances) and the predictor variable described as the intervention (Medication therapy management). The literature review will focus on the definitions, prevalence, issues in the measurement of polypharmacy, and gaps in the literature will be discussed. The implications for research will be drawn from the findings of the literature review.

CHAPTER 2: LITERATURE REVIEW

2.1 HIV/AIDS

Human Immunodeficiency Virus (HIV) is a virus that infects the human immune system and causes immunosuppression by destroying the CD4+ T lymphocytes. HIV can be spread through contact with body fluids such as blood, pre-seminal fluid, semen, vaginal fluids, rectal fluids, and breast milk. The virus is transmitted primarily through genital sexual contact but can also be transmitted through non-sexual routes, such as mother to child transmission, and injection drug use (M.-B. Huang et al., 2015). The predominant mode of transmission of HIV in the US is from men who had sex with men (MSM) and through injection drug use (UNAIDS, 2015). Once HIV infection occurs, it progresses through four stages (see figure 1) (Anthony S Fauci, Schnittman, Poli, Koenig, & Pantaleo, 1991).

The first stage is the primary infection, where the virus multiplies rapidly in the plasma, followed by a sharp decrease in the number of CD4+ T-cells in the peripheral blood. The second stage manifests clinically with acute symptoms that may last for 3 to 4 weeks with a rapid increase in the viral load. This is followed by the third stage, where the body develops a cellular and humoral immune response to the virus, with a decrease in detectable viremia. This stage is a period of clinical latency that may last for up to 10 years. During this period, the patient is usually asymptomatic (Anthony S Fauci et al., 1991). The

CD4+ T-cell count continues to decrease during these years until it reaches a critical level where there is an increased risk of opportunistic infections and cancers. This is the fourth stage, where AIDS occurs (Pantaleo, Graziosi, & Fauci, 1993). The progression of HIV infection when untreated leads to AIDS (Anthony S Fauci, 1999). CD4 counts are used as a measure to monitor immunologic response once therapy is started.

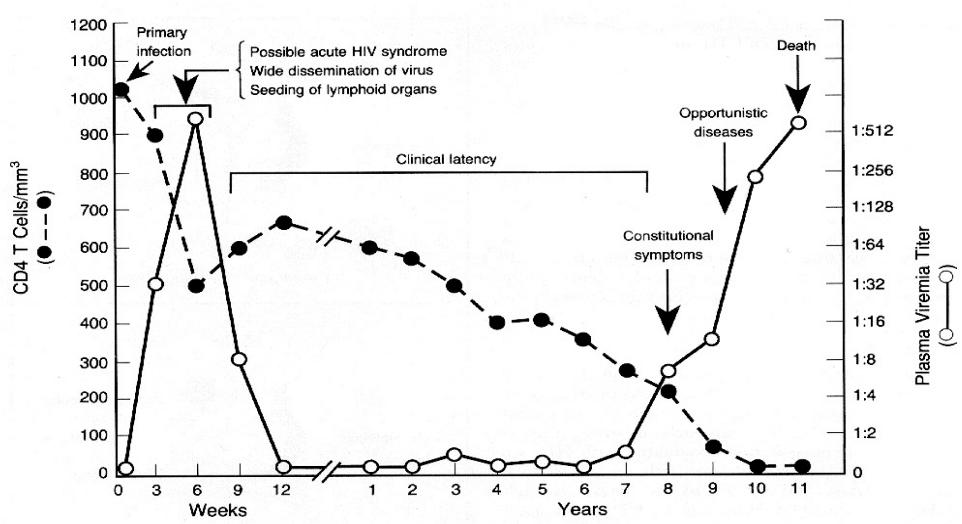

Figure 1 Stages of HIV

There is currently no cure or vaccine for HIV infection because the virus undergoes much evolution, thereby making it resistant to treatment (Levin, Bull, & Stewart, 2001). However, medical advances have led to the development of highly active antiretroviral therapy (HAART) to help reduce the viral load (amount of HIV in the blood) and improve the quality of life of people with the disease (WHO, 2016). With appropriate and consistent use of antiretroviral drugs (ARV), people infected with HIV an expected lifespan that is slightly shorter than healthy individuals with no HIV (Nasi et al., 2017). Their prolonged existence makes them susceptible to having other chronic diseases which is caused by the

chronic inflammation and activation of the immune system (Deeks, 2011; Greene et al., 2014; Nasi et al., 2017). The literature suggests that the risk of non-AIDS related morbidity is higher among HIV-infected patients who are on antiretroviral therapy when compared to their age-matched uninfected peers due to factors related to HIV or the treatment of HIV (Bhaskaran et al., 2008; Deeks, 2011; Losina et al., 2009). The increased risk of comorbid disease in PLWHA increases their risk of polypharmacy. It is, therefore, essential to evaluate the impact of interventions such as medication therapy management on polypharmacy in people infected with HIV/AIDS.

2.1.1 HIV history and Epidemiology

To accurately describe polypharmacy in people infected with HIV in the US, it is important to have some knowledge about the history and epidemiology of HIV. The history of HIV/AIDS in the US dates back to 1981 when the first cases of illness related to AIDS were reported in California among five homosexual men treated for Pneumocystis carinii pneumonia in three Los Angeles hospitals. These men showed evidence of T-lymphocyte depletion (CDC, 1982). Within a year of identifying the disease, the Centers for Disease Control (CDC) had received reports of over a thousand persons with AIDS in the US. The mortality rate was about 39 percent. It was not until 1983 that HIV was identified as the causal agent of AIDS (Blattner, Gallo, & Temin, 1988; UNAIDS, 2015). Since the discovery of HIV, medical advances and programs have been implemented to prevent the spread of the disease and care for those infected. These interventions have led to a steady decline in the incidence of HIV cases. The incidence of HIV in the US has remained at less than 50,000 cases per year for over a decade. (CDC, 2018; Hall et al., 2008; Hall et al., 2017; M.-B. Huang et al., 2015).

It is estimated that about 36.7 million people living with HIV globally (CDC, 2018). The CDC estimated that about 1.1 million people in the United States in 2015 are living with HIV. The same data also showed about 77% of people living with HIV in 2015 were males, while 23% were females. 52% of this population were men who had sex with men, which makes it the most common route of transmission

in the US. The most recent data also showed that the most predominant race affected were blacks (42%), and 31% of those infected were aged 45-54 years (CDC, 2018). This information is crucial because studies have shown that chronic diseases have increased prevalence with aging (Nasi et al., 2017). They are, therefore, more likely to be using multiple medications simultaneously. Results also show that males (11.9%) had a higher proportion of undiagnosed HIV when compared to females (2.6%). Also, people in age groups 25-34 years had a higher proportion of undiagnosed HIV when compared to other age groups (CDC, 2018).

In the US, the geographic distribution of HIV/AIDs differs across states and regions. The rate (the number of cases per 100,000 people) of persons living with an AIDS diagnosis was highest in the Northeast, followed by the South, the West, and then the Midwest in the year 2008 (see figure 2) (CDC, 2018).

Geographic distribution of AIDS in the United States

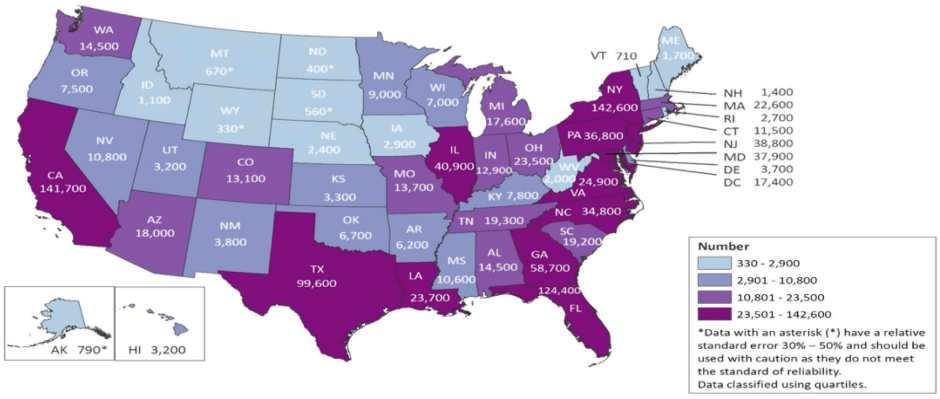

Figure 2 Geographic distribution of AIDs in the United States

By region, the Southern region of the United States account for about half of HIV diagnosis in the US. The map in figure 2 shows the estimates of HIV prevalence in people older than 13 years in the United

States in 2015. HIV prevalence was highest in California, Florida, Georgia, Illinois, Louisiana, Maryland, New York, New Jersey, North Carolina, Pennsylvania, Texas, and Virginia. Fifty percent of persons living with HIV infection are accounted for by five states: California, Florida, Georgia, New York, and Texas (CDC, 2018).

Although HIV exists in most states in the US, there is a report of a decrease in the incidence of HIV in the US due to improvement in HIV intervention programs. The estimated incidence of HIV in the US decreased from 52,721 in the year 2003 to 39,651 in 2010. The incidence also decreased in males from 38,164 to 33,035, and among females from 13,557 to 6,616 (Xia et al., 2017). Although there is a decreasing incidence of HIV infection, the disease is still prevalent, and there is a need to investigate the impact of the medication regimen used in PLWHA, especially in states with the most prevalence of the disease.

The MTM services in this study were conducted in 6 out of the most prominent states with cases of HIV/AIDS —Georgia, New York, Florida, Illinois, California, and Pennsylvania.

2.1.2 Symptoms of HIV infection

People infected with HIV develop flu-like symptoms such as fever, chills, or rash within 2 to 4 weeks of infection. The symptoms may last for a few days to several weeks. After the earliest stage of HIV, the virus continues to multiply at very low levels and may remain asymptomatic for up to 10 years, even without treatment. (G. Huang, Takeuchi, & Korobeinikov, 2012). The complications of HIV infection can affect every organ in the body. Some infections may occur at any CD4 count, while others may occur when the CD4 count drops below a certain level. HIV symptoms may be protean and non-specific and are typically a combination of symptoms rather than a symptom suggestive of a single disease (Henn, Flateau, & Gallien, 2017).

HIV infection progresses to AIDs after severe damage to the immune system and depletion of the CD4 count. Typically, a person is considered to have AIDS when the CD4 count is less than 200 copies/ml. AIDS is characterized by a plethora of symptoms such as fever, weight loss, fatigue, cough, diarrhea, night sweats, amongst others (T. Quinn, 1984). It manifests with the occurrence of multiple opportunistic infections. Some of these diseases may include oral thrush, oral hairy leukoplakia, bacillary angiomatosis, Kaposi sarcoma, chronic diarrhea, tuberculosis, histoplasmosis, squamous cell carcinoma of the cervix or anus, brain abscess, dementia, pneumocystis pneumonia, meningitis, esophagitis, retinitis, colitis, non-Hodgkin's lymphoma, CNS lymphoma, Mycobacterium Avium Complex (T. Quinn, 1984). The myriads of diseases that occur with HIV requires the use of multiple drugs simultaneously for treatment of these diseases. The life cycle of the virus better explains the occurrence of the signs & symptoms of HIV/AIDs after its penetration into human blood.

2.1.3 HIV Life Cycle

The structure of HIV is depicted in figure 3. It has two molecules of RNA and three structural genes (Env, Gag, and Pol proteins). The env proteins codes for the external envelope protein and comprise of gp120 and gp41. Gp120 is used by the virus to attach to the host cell, while gp41 is for fusion and entry. Both envelope glycoproteins are formed from the cleavage of gp160. The variability in HIV strains occurs in the viral envelope, thereby making it difficult for the body to develop neutralizing antibodies against the viral envelope. This variability also accounts for the difficulty of developing HIV vaccines (Katz, 2019). HIV capsid has the gag protein called p24, gag protein codes for group antigen protein. Serum concentrations of p24 antigen are high in individuals newly diagnosed with HIV. P24 antigen assays are used as a means of diagnosing primary HIV infection. The body produces an antibody to p24 protein during seroconversion, thereby making the p24 antigen undetectable. Therefore, after seroconversion, measuring p24 antigen levels is no longer a viable means of detecting HIV infection (www.aidsmap.com).

Besides the env and gag proteins, the other structural gene in HIV is the pol proteins. The pol proteins codes for polymerase and are made up of HIV enzymes- reverse transcriptase, aspartate protease, and integrase. These enzymes carry out the steps of replication and integration of HIV in the body. Reverse transcriptase, which is also known as RNA-dependent DNA polymerase, synthesizes double-stranded DNA from the viral single-stranded RNA, and it is used to replicate within into the human genome (Kumar, 2005; Sluis-Cremer, Wainberg, & Schinazi, 2015).

HIV Structure

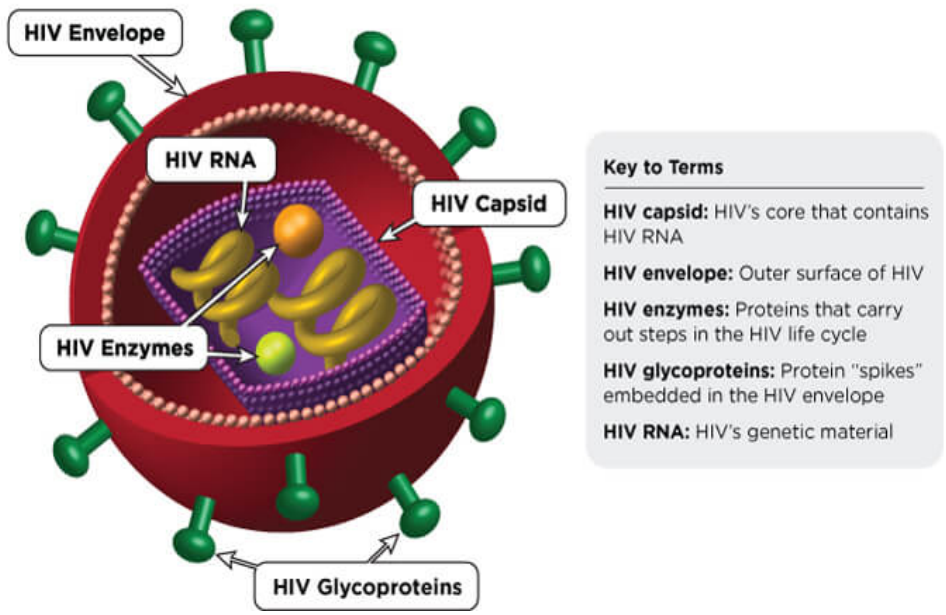

Figure 3 HIV structure

The HIV Life Cycle

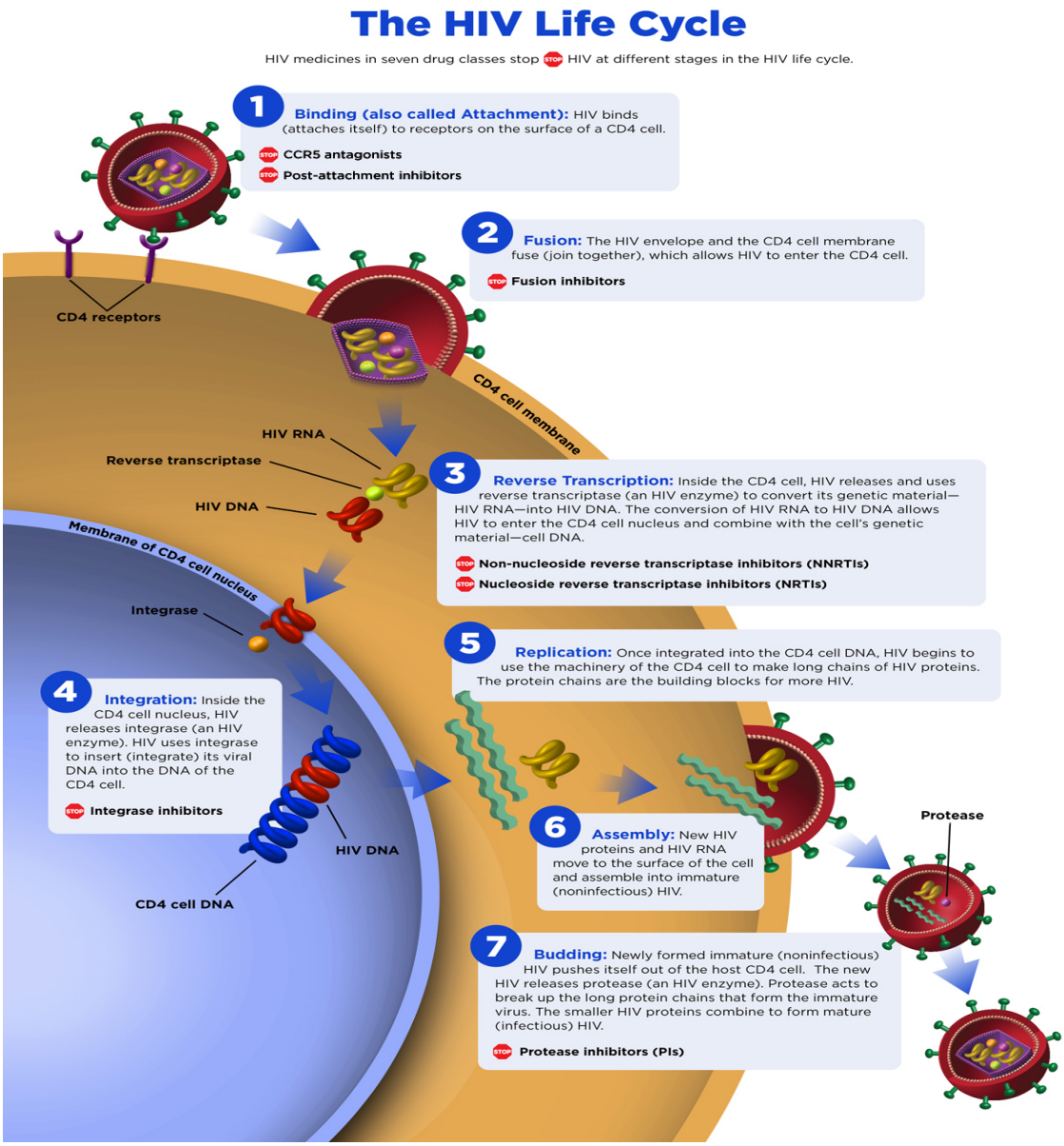

Figure 4 The HIV life cycle

The life cycle of HIV has seven stages, which include binding, fusion, reverse transcription, integration, replication, assembly, and budding (Kumar, 2005). The first stage is the binding stage, where HIV enters the bloodstream and binds to receptors on the surface of a CD4 cell using gp120. Chemokine

co-receptors (CCR5 or CXCR4, or both) are required for entry of the HIV into CD4 cells. Therefore, individuals with CCR5 deletions are less likely to become infected with HIV (Katz, 2019).

Once HIV enters a cell, the HIV envelope and the CD4 cell membrane now fuse to allow HIV to enter the CD4 cell in the fusion stage of the life cycle. HIV then releases the reverse transcriptase enzyme to convert its genetic material from HIV RNA to HIV DNA. This conversion allows HIV DNA to enter the CD4 cell nucleus and combine with the cell's DNA. After it is integrated into the CD4 cell, HIV uses the machinery of the CD4 cells to replicate and make long chains of HIV proteins. These chains serve as the building block for making more HIV. This stage is followed by the assembly stage, where the newly formed HIV protein and HIV RNA moves to the surface of the cell and assemble into immature HIV that is non-infectious. The newly formed immature HIV pushes itself out of the host CD4 cell and releases protease. Protease breaks the long protein chain of the immature virus to form smaller HIV proteins. These smaller proteins combine to form mature (infectious) HIV. Figure 4 shows the different stages of the HIV life cycle (Aids info, 2018). HIV RNA counts have been used as a marker of viral load. It indicates viral burden or viral suppression. An HIV infected person with an HIV RNA count of less than 500 copies/ml is considered to be virally suppressed. Similarly, CD4 counts are used as a marker of immunologic response to treatment. If the level of CD4 count falls below 200 cells/mm^3, the person is considered to be immunosuppressed.

It is essential to understand the immunopathogenic mechanisms of the life cycle of HIV in the body after infection because this knowledge is fundamental to the development of effective therapeutic agents for managing HIV. Antiretroviral medications have been developed to target HIV infection at every stage of its life cycle to reduce its replication in the human body. Hence the need to sometimes use multiple HIV medications in people infected with the disease.

2.1.4 Genetic Variants of HIV

There are two types of HIV: HIV types 1 and 2 (HIV-1 and HIV-2). HIV-1 is closely related to the Simian immunodeficiency virus (SIV) found in chimpanzees, while HIV-2 is closely related to SIV found in sooty mangabeys. There is a belief that the first cases of both virus types were due to cross-species transmission (Sharp, Bailes, Robertson, Gao, & Hahn, 1999). Both HIV types were initially discovered in Africa. HIV-1 is more virulent than HIV-2 (Marlink et al., 1994), and this may be due to the high degree of genetic variation in HIV-1.

HIV-1 has three genetic subgroups: major (M), Outlier (O), and non-major-non-outlier (N) (Alaeus, Lidman, Björkman, Giesecke, & Albert, 1999). Group M is the most prevalent form of HIV-1, and it has been reported to infect millions of people globally. Group N and Group 0 represents less than 1% of global HIV infections, and it is more prevalent in African countries (Alaeus et al., 1999; Peeters et al., 1997). Group M of HIV-1 is further subdivided into ten genetic subtypes (A-J) with subtype B being more predominant in the US and Europe. In contrast, subtypes A, C, and D are more prevalent in Africa. Similarly, subtype E is prevalent in Asia, while subtype C is common in India (Alaeus et al., 1999). These different subtypes attach to different chemokine co-receptors to enter CD4 cells, thereby accounting for differences in their transmissibility, virulence, and tissue tropism (Tscherning et al., 1998).

These genetic variations have also been linked to resistance to HIV drugs and treatment failure. A study reported protease inhibitor resistance-based ART failure in people with HIV-1 subtype A who had no protease drug resistance mutation. The study identified that the protease inhibitor resistance was due to the differences in seven amino acids in gp41 and gag protein in HIV, contributing to a multi-gene mechanism of drug failure (Coetzer, 2017). These genetic variations in HIV subtypes are a reason for the use of different HIV medications in different parts of the world.

2.2 HIV medications

Antiretroviral therapy is used to suppress HIV replication to reduce viral load to below 50 HIV RNA copies/ml. The use of combined antiretroviral agents that target the virus at different stages of its life cycle has a profound effect on the natural history of HIV. Research has shown that when antiretroviral medication is initiated and maintained early in the course of the disease, the life expectancy of people infected with HIV is almost similar to that of their uninfected counterparts (Gulick et al., 1997).

The Center for Disease Control and Prevention (CDC), therefore, recommends that treatment should be initiated early in HIV patients regardless of their CD4 count. They also suggest that once treatment with antiretroviral therapy begins, it should be continued indefinitely to prevent increased levels of HIV in the blood (Dybul, Fauci, Bartlett, Kaplan, & Pau, 2002). A randomized clinical trial showed that there is a greater than 50% risk reduction in mortality from HIV infection when treatment is started immediately compared to when HIV treatment is delayed until the CD4 count is <350 cells/μl (InsightStartStudyGroup, 2015).

Besides the use of antiretroviral therapy for HIV, treatment of people with HIV also include providing prophylaxis to prevent opportunistic infections, malignancies, and other complications of HIV as well as providing medications for treating opportunistic infections and other complications of HIV.

There are five major categories of antiretroviral therapy, and it is recommended that initial treatment for HIV should consist of three or more medications from two different classes to reduce the risk of developing resistance. The major classes of HIV medications are: These seven classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, and a CD4 T lymphocyte (CD4) post-attachment inhibitor. In addition, two

drugs, ritonavir (RTV) and cobicistat (COBI) are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK pro les of PIs and the INSTI elvitegravir (EVG) (NIH, 2019).

The currently preferred regimen for HIV treatment includes a combination of two NRTIs administered with a third active ARV drug from one of three classes either an Integrase strand transfer inhibitor INSTI, or a NNRTI, or a PI, inhibitor with a pharmacokinetic (PK) enhancer such as cobicistat or ritonavir (NIH, 2019). The choice of HIV regimen for any individual determined by the presence of comorbidities, medication side effects, interactions with concomitant medications, convenience, and genotypic drug-resistant testing (aidsinfo.gov, 2018).

NNRTI's are the second class of antiretroviral medications approved by the FDA for the treatment of HIV in 1989. NNRTI act as a non-competitive inhibitor of the HIV-1 reverse transcriptase enzyme. It induces conformational changes in the reverse transcriptase enzyme thereby reducing its catalytic activity (de Béthune, 2010). It inhibits RNA-dependent and DNA-dependent polymerase function of the reverse transcriptase enzyme, thereby inhibiting the replication of HIV. The earliest approved first-generation NNRTIs are nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). The second-generation NNRTI's are etravirine (ETR) and rilpivirine (RPV) and Doravirine that was recently approved by the FDA (aidsinfo.gov, 2018).

Resistance to NNRTI's develop when there is a mutation in the reverse-transcriptase enzyme. Resistance to one type of NNRTI can be transferred to another. Also, resistance can be transmitted from mother to infant when there is an infection of a drug-resistant strain of HIV (de Béthune, 2010). NNRTI's are prone to resistance when used as a monotherapy or when treatment is suboptimal. They are, therefore, combined with NRTI's or PIs to reduce cross-resistance (Usach, Melis, & Peris, 2013). Examples of fixed-dose combinations of NRTI with other class of antiretroviral medicines are: Efavirenz + tenofovir + emtricitabine (Atripla), Rilpivirine +Tenofovir+ emtricitabine (Complera), Dolutegravir+ rilpivirine (Juluca) (Aidsetc.org, 2018)

The reported side effects of NNRTIs include CNS side effects such as headache, dizziness, impaired concentration, vivid dreams, and insomnia. Other side effects are hepatotoxicity, nausea, diarrhea, and rash. These side effects are enhanced when used with other non-HIV medications (Tseng & Foisy, 2012), hence the need for further studies on polypharmacy in people with HIV.

2.2.3 Protease inhibitors

Protease inhibitors prevent the cleavage of gag and gag-pol protein precursors by the HIV protease enzyme. The protease enzyme cleaves amino acid sequences in the gag-pol polyproteins to enable the maturation of nascent viral particles (virions). Therefore, protease inhibitors arrest the maturation and prevent the infectivity of budding HIV (Flexner, 1998). Their primary action is to prevent subsequent waves of HIV infection. Examples of FDA approved PIs are darunavir, ritonavir, lopinavir (ABT-378), atazanavir, nelfinavir, indinavir, saquinavir, fosamprenavir, tipranavir, and amprenavir.

The reported side effects of PIs include a decrease in bone marrow density, intracranial hemorrhage, kidney stones, dyslipidemia, lipodystrophy, diarrhea, nausea, vomiting, insulin resistance, and drug-induced hepatitis (aidsinfo.gov, 2018; Carr et al., 1998). PIs can interact with medications that are inhibitors or inducers of cytochrome P-450 to increase or decrease its concentration in the plasma (Piscitelli, Flexner, Minor, Polis, & Masur, 1996). Therefore, the use of PIs with other medications may increase the risk for drug-drug interaction or drug toxicity, which justifies the need for this study.

Similarly, the highest risk of resistance to HIV is seen with PIs because the HIV protease enzyme can undergo multiple mutations leading to a high level of drug resistance (Flexner, 1998). PIs are, therefore, not recommended for use as a monotherapy (aidsinfo.gov, 2018). The current guideline recommends that PIs should be combined with two NRTIs. Clinical trials have also demonstrated that the combinations of PIs with nucleoside analogues can cause prolonged suppression of viral load. Examples of approved fixed-dose combinations of PI are: darunavir + cobicistat + emtricitabine + tenofovir (SYMTUZA), lopinavir + ritonavir (Kaletra), and Darunavir + Cobicistat (Prezcobix). Cobicistat is a

pharmacokinetic booster used to increase the blood levels of HIV medications. It has also been shown that treatment regimens containing a PI are among the most potent against HIV but often have the least tolerable side effects (aidsinfo.gov, 2018). Therefore, when assessing the risk associated with polypharmacy, it is critical to identify each drug component to predict the likelihood of drug interactions better.

2.2.4 Entry inhibitors

Entry inhibitors are medicines designed to block the initial step of HIV infection by targeting the different stages of entry of HIV into human white blood cells. They consist of fusion inhibitors, chemokine co-receptor antagonists and a monoclonal antibody. An example of fusion inhibitors is enfuvirtide. It acts by blocking the attachment of the viral gp120 to the CD4 T cell receptor and the fusion of viral and cellular membranes (Briz, Poveda, & Soriano, 2006). Enfuvirtide is injected parentally twice daily, thereby making its long-term use cumbersome. The reported side effects of enfuvirtide are injection site hypersensitivity reactions and increased risk of pneumonia (Reust, 2011). Resistance to entry inhibitors develops when there are multiple changes within the viral envelope protein (gp120) (Briz et al., 2006).

The second class of entry inhibitor is the chemokine co-receptor antagonists, which acts by inhibiting the binding of HIV gp120 to CCR5 or CXCR4 co-receptors. HIV gp-120 needs to bind to chemokine co-receptors after binding to CD4 cells to be able to enter the cell. An example is maraviroc, which acts by inhibiting the binding of viral gp120 to CCR5. Resistance to maraviroc develops when the virus changes its co-receptor to CXCR4 (Briz et al., 2006). The side effects associated with maraviroc are bronchitis, nasopharyngitis, esophageal candidiasis, rash, abdominal pain, musculoskeletal symptom, and hepatotoxicity.

The third class of entry inhibitor is the humanized IgG4 monoclonal antibody, which acts by blocking HIV from infecting CD4 cells. It binds to the second domain of the CD4 receptor and interfere

with the post attachment step that allows HIV particles to enter host cell. It prevents the transmission of the virus that occurs through cell-cell fusion. It however does not interfere with CD4-mediated immune function (NIH, 2019). An example of this class of drug is Ibalizumab. Resistance to Ibalizumab has not been reported. The side effects associated with Ibalizumab are rash, diarrhea, headache, nausea, dizziness, depression, and immune reconstitution inflammatory syndrome (NIH, 2019).

2.2.5 Integrase inhibitors

Integrase inhibitors prevent the integration of HIV into the host chromosome and viral replication by blocking the action of integrase. Integrase is an enzyme in HIV that catalyzes the insertion of proviral DNA into the genome of infected host cells (Pommier, Johnson, & Marchand, 2005). Integrase interacts with the reverse transcriptase enzyme and can regulate the reverse transcription process. Therefore, the drugs in this class inhibit one of the processes required for viral replication, and is effective in reducing the viral load (Steigbigel et al., 2008). Raltegravir was the first integrase inhibitor approved in 2007. Other integrase inhibitors are elvitegravir, and dolutegravir. Resistance to integrase inhibitors develops easily when there is a mutation in the integrase enzyme, thereby limiting its long-term effectiveness. Some of the reported adverse effects of raltegravir are myopathy, rhabdomyolysis, diarrhea, nausea, and headache (Reust, 2011). Besides the use of antiretroviral therapy, HIV patients are also given other medications at different stages of the disease to prevent and treat opportunistic infections and malignancies.

2.2.6 Prophylactic medications against opportunistic infections in HIV

The other class of medicines used by PLWHA are prophylactic medications for preventing opportunistic infections. Trimethoprim-Sulfamethoxazole (TMP-SMX) is used for prophylaxis against Pneumocystis Carinii Pneumonia (PCP). Dapsone plus pyrimethamine plus leucovorin can also be used as an alternative PCP prophylaxis or in people with Toxoplasmosis. Valganciclovir is used for preventing cytomegalovirus (CMV) infection. Oseltamivir is used for influenza. It is recommended that PLWHA

with latent tuberculosis (TB) should take Isoniazid for nine months to prevent the development of active TB. Azithromycin or Clarithromycin is recommended for PLWHA as prophylaxis against Mycobacterium Avium Complex (MAC). Itraconazole is used as prophylaxis for histoplasmosis. Fluconazole or itraconazole is used for the prevention of coccidioidomycoses in people with low CD4 counts <250 cells/µl (Benson et al., 2009). Other medications used by PLWHA are those used for treating opportunistic infections, complications of HIV, and other comorbid diseases. These medications will not be discussed extensively in this article.

It is important to note that although the use of the prophylactic medications mentioned above with antiretroviral therapy has been shown to improve the health of people with HIV, these medications also contribute to polypharmacy. Therefore, health care professionals, caregivers, patients, and the public should be aware of the possible risk of adverse effects and drug interactions that may occur in PLWHA when using multiple medications simultaneously.

2.3 HIV medications and Comorbidity

Besides the fact that HIV patients have increased risk of comorbidities, some antiretroviral medicines have side effects that predispose them to have other chronic diseases. More medications are needed to treat the comorbidities in HIV patients, thus causing an increase in polypharmacy. Cardiovascular disease, renal disease, and diabetes are mostly linked to ARTs.

2.3.1 Cardiovascular disease

Studies have suggested that there is an increase in the prevalence of the risk factors for chronic diseases such as smoking, heavy alcohol use, and lipid disorders in the HIV infected population when compared to the general population (Glass et al., 2006; Mondy et al., 2007). However, other studies have shown an association between the use of some HIV medications and increased risk for cardiovascular

diseases (CVD) and other chronic diseases despite the preexisting risk factors. CVD accounts for about ten percent of deaths in people with HIV (Reust, 2011). A cohort study on 23,437 HIV-1 infected subjects reported an increased incidence rate of myocardial infarction in subjects exposed to protease inhibitors when compared to those not exposed after adjusting for known cardiovascular risk factors. Relative rate [RR]=1.16 (95% [CI], 1.10 to 1.23) (DADStudyGroup et al., 2007).

Similar studies have shown that the prolonged use of some combination antiretroviral therapy is associated with the increased risk of developing myocardial infarction. The medications implicated are indinavir, and ritonavir, abacavir, and didanosine (DataCollectiononAdverseEventsofAnti-HIVDrugsStudyGroup, 2003; Worm et al., 2010).

2.3.2 Renal diseases

Besides the reported risk of CVD with HIV medications, some antiretroviral therapy and prophylactic medications used by HIV patients have also been associated with the increased risk of chronic renal disease. Although HIV is known to cause HIV associated nephropathy (HIVAN) (Rao, Friedman, & Nicastri, 1987), studies have shown an association between antiretroviral medicines like tenofovir and indinavir and the increased risk of chronic renal failure (Mocroft et al., 2007). Tenofovir causes impairment in renal function, which manifests as increased serum creatinine, glycosuria, hypophosphatemia, hypokalemia, and urinary phosphate wasting. Indinavir is associated with increased serum creatinine, renal atrophy, pyuria, or hydronephrosis (aidsinfo.gov, 2018). Diseases related to renal failure such as Vitamin D deficiency, osteopenia, and osteoporosis are also more common in patients with HIV infection.

2.3.3 Diabetes mellitus and Insulin resistance

In addition to the adverse effects of HIV medications mentioned above, some ART medicines have metabolic complications, which include insulin resistance, hyperlipidemia, and lipodystrophy,

thereby increasing the risk of developing type 2 Diabetes mellitus (Brown et al., 2005; Samaras, 2009). Zidovudine, Stavudine, Didanosine, Indinavir and Lopinavir have reported side effects of impaired glucose tolerance (aidsinfo.gov, 2018). A study by Behrens et al. demonstrated an association between the use of protease inhibitors and impaired glucose tolerance and insulin resistance. The study reported beta-cell dysfunction estimated by measuring the responses of insulin, proinsulin, and C-peptide to an ingested glucose load in HIV patients treated with protease inhibitors compared to those who were not treated (Behrens et al., 1999). This example indicates that drug-disease interactions are a common occurrence in PLWHA. Also, the increased susceptibility of people with HIV/AIDS to having multiple diseases simultaneously puts them at high risk for polypharmacy.

2.4 Polypharmacy

The World Health Organization (WHO) defined polypharmacy as " the administration of many drugs at the same time to an individual or the administration of an excessive number of drugs" (Monégat, Sermet, & Rococo, 2014). Polypharmacy can be therapeutically beneficial for some patients but can be harmful if poorly managed. Hence researchers coined the terms- "appropriate and inappropriate polypharmacy" (J. K. Aronson, 2006; Duerden et al., 2013). Polypharmacy may be considered appropriate when the use of medications is considered optimal, and the medications are prescribed to people with concomitant pathologies or complex medical situations according to the best evidence. In contrast, polypharmacy is inappropriate when the anticipated benefits for the patient are not obtained or when the medications are inappropriately prescribed (Duerden et al., 2013). Polypharmacy becomes a problem when the drug combination is hazardous or when the demands of taking the medications is considered as a burden by the patient. It is also a problem when the increased pill burden impairs medication adherence or when there is a need to prescribe more medicines to treat the side effects of other medicines.

Polypharmacy is becoming increasingly common in primary and secondary care due to the growth of an aging population and the increasing prevalence of multiple chronic diseases in an individual. Several explanations have been given for the increasing prevalence of polypharmacy. People with asymptomatic chronic diseases such as hypertension are being treated with multiple medicines to prevent complications such as stroke and acute myocardial infarction (Freiberg et al., 2013). Also, in people with chronic diseases, polypharmacy may result from the lack of coordinated care among health care professionals who manage chronic diseases. Physicians tend to follow evidence-based guidelines for managing each of the multiple diseases that affect an individual. They prescribe medications for each disease, and the patients end up with a complicated combination of drugs. The guidelines for treating chronic diseases did not take account of long-term conditions that co-exist, such as hypertension, diabetes, coronary heart disease, heart failure and chronic obstructive pulmonary disease, and how these may result in polypharmacy. Medications should be prescribed in a way that explicitly considers the overall effects of the total drug regimen rather than the individual drugs, but this is not currently the case.

2.4.1 Epidemiology of Polypharmacy

Polypharmacy is prevalent in the United States and occurs in 10% of the general population and 30% of older adults (K. J. Quinn & Shah, 2017; Varghese & Koya, 2019). Polypharmacy is a significant public health issue in the United States. It is driven by the high rate of chronic diseases, such as cardiovascular disease, cancer, type 2 diabetes, arthritis, and osteoporosis (Fulton & Riley Allen, 2005; Hunt, Kreiner, & Brody, 2012; Payne & Avery, 2011).

Polypharmacy in the United States

Multiple studies have focused on the prevalence of polypharmacy and the factors that may influence medication utilization in people with chronic diseases. An analysis of data on the use of medicines in the United States in 2013 showed that in America, the average use of medication per person is about 12.2 prescriptions (Aitken, Kleinrock, Lyle, & Caskey, 2014). **See Figure 5**

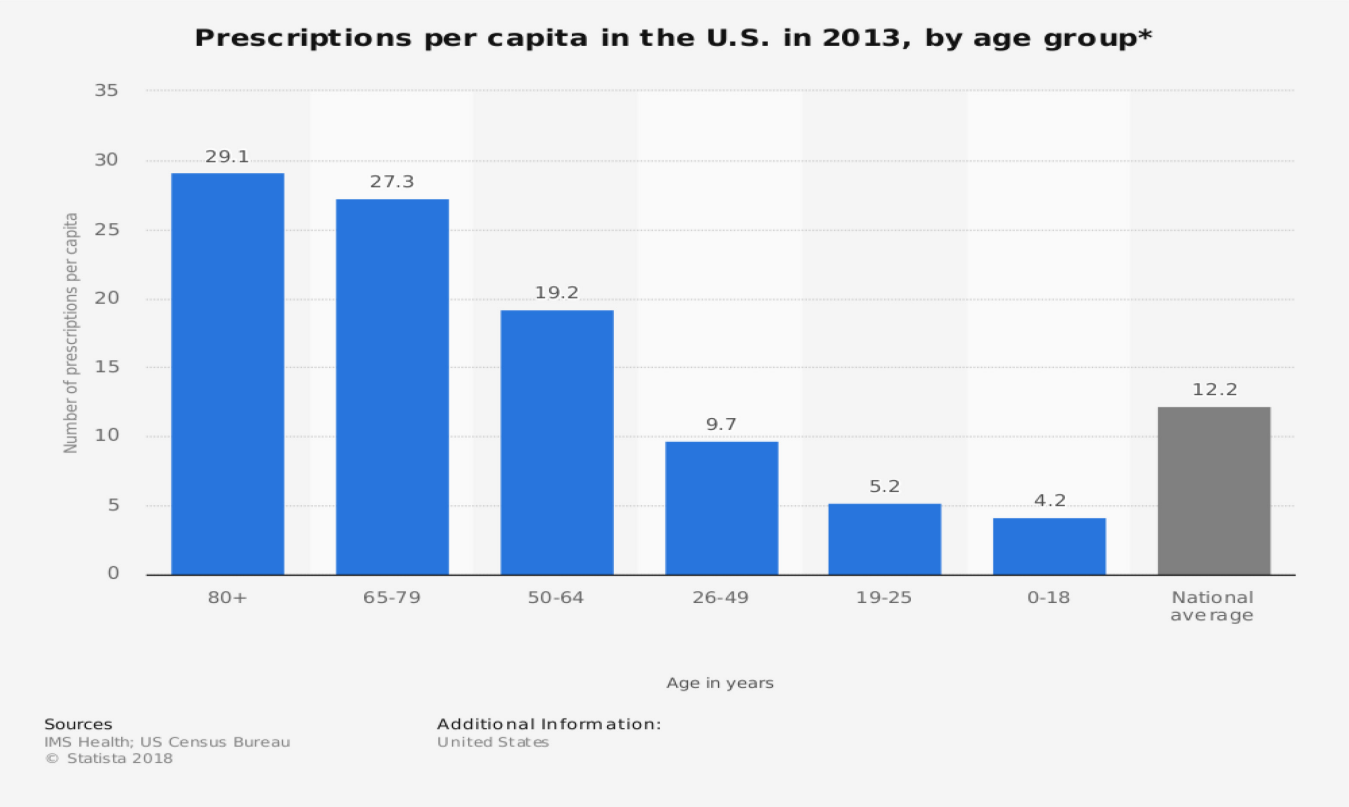

Figure 5 Prescriptions by age group in the US in a year

Figure 5 shows the number of prescriptions per person per year in the United States in 2013 by patient age group (Statista, 2014). The graph shows that the average prescription per person in adults between 50 to 64 years is 19.2 in 2013. The elderly 80 years and above have the highest number of medications prescription refill in a year (an average of 29 prescriptions per person.

Kantor et al. tried to evaluate the trend in prescription drug use using nationally representative data from the National Health and Nutrition Examination Survey (NHANES) from 1999-2000 to 2011-2012 among 37,959 US adults aged 20 years or older. The study showed an increase in the prevalence of polypharmacy (defined as five or more drugs) from 8.2% in 2000 to 15% in 2012 (Kantor et al., 2015).

Another study used the Medical expenditure panel survey to describe the prevalence of polypharmacy among 5216 cancer survivors and 19,588 non-cancer controls. The study estimated the prevalence of polypharmacy among cancer survivors to be about 64% among cancer survivors and 52% among non-cancer controls. (Kantor et al., 2015)

A cross-sectional study on the 2004 national nursing home survey defined polypharmacy as the concurrent use of 9 or more medications. The prevalence of polypharmacy was estimated to be approximately 40% (Dwyer, Han, Woodwell, & Rechtsteiner, 2010). Similarly, a study using NHANES data from 1988 to 2010 estimated the prevalence of polypharmacy among 13,869 adults aged 65 and over to increase from 12.8% to 39% (Charlesworth, Smit, Lee, Alramadhan, & Odden, 2015).

2.4.1.1 Prevalence of polypharmacy in PLWHA

There is limited literature using a nationally representative sample to estimate the overall prevalence of polypharmacy in PLWHA in the US. However, studies have estimated the prevalence of polypharmacy in different subjects and settings. A study using the national ambulatory health care survey estimated that the prevalence of polypharmacy among PLWHA in the US has increased from 16% in 2006 to 35% in 2010(Moore, Mao, & Oramasionwu, 2015). A prospective cohort study among men sleeping with men in 4 US regions reported the prevalence of polypharmacy in HIV positive males to be 24.4% (Ware et al., 2018). Likewise, a cross-sectional study of 2,112 persons with HIV in 24 countries estimated the prevalence of polypharmacy to be 42.1 percent (Okoli et al., 2020). All the reported prevalence indicate that polypharmacy is increasing and should be monitored.

2.4.1.2 Factors influencing the increasing prevalence of polypharmacy

Several factors could be contributing to the increasing prevalence of polypharmacy. Some of these factors are at the patient-level, the systems-level, and the provider-level. Patient-level factors such as socioeconomic status, lack of adequate education, and aging could contribute to the increasing

prevalence of polypharmacy (Carmona-Torres et al., 2018; Fulton & Riley Allen, 2005). Increased age is associated with the increased prevalence of chronic diseases. Longitudinal studies have shown the rise in the number of prescribed medications with aging (Guthrie et al., 2015; Kantor et al., 2015). Also, self-medication and the use of over the counter medicines will contribute to polypharmacy (Duerden et al., 2013; Guthrie et al., 2015). Specific patient-level factors in the literature that have been identified in people living with HIV/AIDS that are associated with polypharmacy include aging, gender, lack of understanding of drug regimen, recreational drug use and suboptimal adherence (Edelman et al., 2013; Furler, Einarson, Walmsley, Millson, & Bendayan, 2004; Gianotti et al., 2013; Gleason, Luque, & Shah, 2013; Greene et al., 2014; Holtzman et al., 2013; Sanfélix et al., 2008; Siefried et al., 2018; Tseng, Szadkowski, Walmsley, Salit, & Raboud, 2013; Ware et al., 2018).

The factors at the systems-level include the development of new therapies and technologies, thereby increasing the discovery of conditions that need to be treated with medications. Also, the development and increased use of primary and secondary preventive strategies have led to the increased use of medications (Gorard, 2006). Also, health care workers have limited guidance or experience as to how to approach care decisions for patients with multiple comorbidities. Medical training and clinical care encourage the use of guidelines for treating single diseases.

At the provider-level, clinical guidelines for managing diseases are focused on single conditions and does not account for the increasing number of patients with multiple comorbid conditions (Duerden et al., 2013). Patients with multiple chronic diseases may require specialist care and visit multiple physicians for treatment. The absence of continuity of care and information sharing among health care professionals may result in polypharmacy (Carmona-Torres et al., 2018; Duerden et al., 2013). The challenge for health care providers is to provide a safe and evidence-based medication regimen that minimizes the risk of adverse effects. To achieve this outcome, health care providers must identify the risks associated with polypharmacy and implement strategies to reduce it when it is inappropriate. The key to addressing

polypharmacy is to determine the need for the right medication at the right dose and determine the shortest duration of use possible. Regular monitoring and reviewing of patients' medication are necessary for preventing the risks associated with polypharmacy and improving the quality of life.

2.4.2 Criteria used for measuring polypharmacy

In the literature, there is no concise measure of polypharmacy. The common approach is the use of an arbitrary threshold for the number of drugs. Different studies have employed different numbers ranging from the concurrent use of two or more medications to the use of 5-9 medications in describing polypharmacy (Bjerrum, Rosholm, Hallas, & Kragstrup, 1997; Castioni et al., 2017). The table below shows a summary of ways polypharmacy was measured and the prevalence rates in different studies.

Summary of definitions and methods of analysis of polypharmacy and its prevalence				
Authors	Definition & Analysis	Settings/subjects	Exclusions	Prevalence
(Veehof, Jong, & Haaijer-Ruskamp, 2000)	2 or more drugs analyzed as counts		No exclusions	Not specified
(Slabaugh, Maio, Templin, & Abouzaid, 2010)	5 or more drugs for at least one day analyzed as a categorical variable.	349, 689 elderly >65 subjects in Italy	over-the-counter medications, herbal remedies, or dietary supplements.	39%
(Moore et al., 2015)	≥ 5 prescription medicines	National ambulatory healthcare survey 2006 -2010 in adults with HIV vs. Non-PLWH	Nonprescription medicines	16% in 2006 35% in 2010 in PLWHA; Non-PLWHA 24% in 2006; 32% in 2010

(Dwyer, Han, Woodwell, & Rechtsteiner, 2010)	Concurrent use of 9 or more medications	13403 Nursing home residents in 2004	Vitamins and minerals supplements	40%
(Rambhade et al., 2012)	Taking more drug than is clinically necessary (Inappropriate drug prescription)	326 adults attending clinics in Bhopal India	Excluded nonprescription medications	8.73%
(Weaver, Fisher, & Curci, 2005)	>1 medication	Elderly patients in three nursing home	No exclusions	70% using more than 5 medications. 100% using more than 1 medication

There is difficulty in assessing the problems caused by polypharmacy due to the vagueness in its definition. It is however important that any measure of polypharmacy should be interpreted according to the clinical situation. The use of a cutoff point or categories to define polypharmacy allows the loss of information in the analysis. There are some questions that researchers must consider in operationalizing and defining polypharmacy:

1. What should be counted as a medication? Some difficult items to classify include ointments, wound dressings infused with drugs, topical agents, and oxygen.
2. How should drugs with variable dosages and fixed-drug combinations be counted?
3. Is there a need to consider the duration and the frequency of drug use when estimating polypharmacy? e.g., Will a drug used twice a day be counted twice?
4. Should medications be counted as a categorical or a continuous variable?
5. Should intermittent medications such as antibiotics be included in the regularly prescribed regimen?

6. Should over the counter medicines and drugs used occasionally be counted when studying polypharmacy?
7. Should all medication routes be counted, or should only oral medications be considered?
8. Is there a reasonable cut off point to differentiate a low level of drug use from a high level of drug use?

2.4.2.1 Pill count vs. polyactive substances

Due to the lack of a clear definition of polypharmacy in the literature,

some researchers have suggested that using the pharmacologically active ingredients in medications (polyactive substances) may be a better estimate of the prevalence of polypharmacy than using the pill count. A study by Castioni et al., on the prevalence of polypharmacy in a cohort of 4938 middle-aged population showed that the prevalence rate of polypharmacy (defined as five or more pills) increased from 14.7 % to 16.9% when ≥ 5 or more polyactive substance per day was considered. When all polyactive substances were considered, the prevalence of polypharmacy in study participants was 5.1% higher than the rate based on pill count only (Castioni et al., 2017). Another prospective study conducted among 880 cardiovascular patients over ten years showed that the prevalence of polypharmacy using pill count increased from 1.4 % at baseline to 11.9% at follow-up while the same prevalence using polyactive substances increased from 2.4% at baseline to 17.6% at follow up. About 29% of participants in this study were using combination drugs. With the advent of drugs combining multiple pharmacologically active ingredients. The results of these studies indicate that defining polypharmacy by the number of drugs may be underestimating the prevalence of polypharmacy.

2.4.4 Health Implications of Polypharmacy

Polypharmacy can be harmful when it increases the risk of adverse drug reactions, drug interactions, impair medication adherence, and affect the quality of life for patients. Although polypharmacy may be inevitable, sometimes, it may not be a problem when it is necessary and appropriate. However, continuous monitoring is needed to ensure medication safety.

2.4.5 Polypharmacy and adverse drug reactions

Polypharmacy increases the risk of drug-related morbidity, with adverse drug reactions being one of the significant consequences. Adverse drug reactions are a harmful response of the body to medication, which is not anticipated and occurs at a standard therapeutic dose. Adverse drug reactions lead to adverse drug events (an untoward medical occurrence), which may include organ system injuries, fractures, falls, and cognitive decline in the elderly and mortality (Edelman et al., 2013; Monégat et al., 2014). Almost 6.5% of all emergency hospital admissions in the United States comprise of cases of adverse drug events (US) (Guthrie et al., 2015).

In the US, adverse drug reactions cause about four hospitalizations per one thousand people per year (Shehab et al., 2016) and are one of the top ten causes of death (Makary & Daniel, 2016). In older adults, 28% of hospitalizations, over 4 million cases of adverse drug reactions, and 4.6% of deaths annually are directly attributed to prescribed drug use (Bourgeois, Shannon, Valim, & Mandl, 2010). The estimated annual cost associated with the treatment of adverse drug reactions ranges from 30 to 180 billion dollars (Ernst & Grizzle, 2001; Sultana et al., 2013). People with HIV are more susceptible to adverse drug events from polypharmacy due to decreased organ system reserve, ongoing immune dysfunction, and chronic inflammation (Deeks, 2011; Justice, 2010). The aging HIV population is more susceptible to adverse drug effects from polypharmacy due to the increasing prevalence of liver and renal diseases among them (Joshi et al., 2011; Lucas et al., 2007). These diseases predispose them to have altered pharmacodynamics and increase the risk of drug interactions which may cause variable drug

responses in PLWHA and compromise the effectiveness of the antiretroviral therapy (ART) and other drugs used (Greene et al., 2014; Marzolini et al., 2010; Tseng et al., 2013).

2.4.6 Polypharmacy and Potentially inappropriate medicines

Polypharmacy further becomes a problem when the medications are inappropriately prescribed or when the anticipated benefits for the patient are not realized. Polypharmacy increases the risk of potentially inappropriate medications, drug duplication, and drug-drug interactions (Duerden et al., 2013). Potentially inappropriate medications are drugs that have more risks than benefits to the patient. The primary factor that drives the prescription of multiple drugs is the presence of multiple comorbid conditions and the severity of the diseases. The aging of the HIV population predisposes them to have age-related chronic conditions, and subsequently, they receive multiple medications in addition to their antiretroviral therapy. Aging causes physiological changes such as decreased albumin levels, increased fat to lean muscle ratio, decreased metabolism, and excretion, thereby affecting the exposure and responses to drugs. Medications prescribed to this population may not achieve the anticipated benefits because of the way the medication is metabolized, cleared, and stored in the body. Also, the drugs may be inappropriate based on the indication, the potential for side effects, and the drug interaction. It is, therefore, essential to measure the number of medications and monitor the complexity of the drugs taken by people living with HIV. This can only be achieved if the polyactive substance in their medication regimen is known.

Likewise, the synergistic effect of the increased number of non-antiretroviral drugs, the pharmacokinetic properties of antiretroviral drugs, and the metabolic changes associated with aging indicate more risk of drug-drug interactions for PLWHA. Drug-drug interactions are a concern in PLWHA (Holtzman et al., 2013; Marzolini et al., 2010) because antiretroviral drugs act as substrates, inhibitors, and inducers of the enzyme cytochrome P450 which is the primary enzyme that metabolizes drugs (Halloran et al., 2019). A study of 698 people living with HIV and 304 HIV-negative controls

showed that there are three times higher odds of potential drug-drug interaction between non-ARV and ARV drugs in PLWHA when compared to HIV-negative controls. Drug-drug interactions cause drug toxicity.

An increase in the number of potentially inappropriate medicines in a medication regimen may also increase the risk of iatrogenic accidents (Monégat et al., 2014). Iatrogenic accidents are medical errors inadvertently caused by medical personnel. Having multiple prescriptions from different providers could result in the use of drugs that are inappropriately prescribed. Iatrogenic accidents account for about 1.5 percent of admissions in the emergency department and 5 to 25 percent of hospital admissions among the elderly in the US (Monégat et al., 2014). These results show that it is necessary to continually review the medications of HIV patients at the point of contact in each health system.

2.4.7 Polypharmacy and non-adherence to medication regimen

Besides the risk of adverse drug events and increased cost of healthcare expenditure, polypharmacy has also been linked to increased risk of non-adherence to the prescribed medication regimen (Gianotti et al., 2013). The increased pill burden makes patients not to be compliant with their medication intake. Non-adherence to medications among HIV patients is associated with treatment failure and worsening of preexisting comorbidities.

Studies on medication use in chronic diseases suggest that an increase in the complexity of a medication regimen is associated with a decrease in patient adherence (Stone, 2001). With a complicated drug regimen, patient adherence, which is a critical determinant of treatment success and can significantly improve health outcomes, is decreased (Catz, 2000; Guthrie et al., 2015).

Also, some of the studies on medication adherence and polypharmacy considered only oral and prescribed medications for HIV patients (Krentz & Gill, 2016; Tseng et al., 2013). There was no consideration of other medicines administered via the injection, inhalation, and topical routes. Also, over

the counter medications were not considered (Krentz & Gill, 2016). The authors did not discuss the indication of the drugs, and they did not determine if the medications were appropriate for the medical conditions being treated. It is essential to be able to answer these questions to improve understanding of drug-drug interactions in PLWHA. Knowing the indications and appropriateness of the medications used will also help to determine ways of reducing polypharmacy in these patients. Having an accurate account of medication use will also affect the interpretation of the results on the outcome of polypharmacy on medication adherence in PLWHA. This study utilized all medications taken by patients including over the counter medications to increase the accuracy of the analysis.

2.4.8 Economic Implications of Polypharmacy

Polypharmacy is associated with adverse drug reactions, an increase in hospital admissions, increased length of hospital stays and increased healthcare costs for patients and the healthcare system (Budnitz, Lovegrove, Shehab, & Richards, 2011; Tam, Hirsch, & Watanabe, 2017). Out of incident adverse drug reactions that resulted in hospitalization, the cost per adverse drug reaction for each patient admitted was estimated to be $2,262 per adverse drug reaction (Classen, Pestotnik, Evans, Lloyd, & Burke, 1997). There is a variation in cost based on hospital wards. Care of adverse drug events in a non-intensive care unit (ICU) was estimated to be about $13,994 and $19,685 in ICU (Cullen et al., 1997). A more recent study showed that adverse drug events prolong the duration of hospitalization by an average of 2 days with an additional expenditure of about $2,000 to $2,500 (Hughes & Ortiz, 2005).

The cost of drug-related morbidity and mortality was estimated to be between $US30 billion $US130 billion annually (White, Arakelian, & Rho, 1999). In 2001, Ernst and Grizzle demonstrated that the expenditures associated with drug-related problems surpassed $177.4 billion, with drug-related hospitalizations accounting for about 70% of the cost, and long-term-care admissions accounting for about 18%. These estimates indicate the high cost associated with the risks from polypharmacy.

2.4.9 Multiple Chronic diseases and polypharmacy

One other factor that has been reported consistently as a determinant for the use of multiple medications is the presence of multiple comorbid conditions (Calderón-Larrañaga et al., 2012; Mannucci et al., 2014). Comorbidity is the presence of diseases that arise as a complication of the clinical progression of an index disease, while multimorbidity is the presence of an independent chronic disease occurring with the primary index disease in an individual (Mannucci et al., 2014). HIV/AIDS is a disease with the potential for the occurrence of multiple comorbid chronic illnesses. These chronic conditions are common in the general population. However, chronic diseases occur at a faster rate in PLWHA because of immune suppression and the aging of this population. The occurrence of these chronic conditions increases the likelihood of engaging in polypharmacy (Brooks, Buchacz, Gebo, & Mermin, 2012). Polypharmacy is widespread in people with comorbidities because it is a common practice for physicians to follow the guidelines available for each of the multiple diseases that affect an individual. Different physicians prescribe medications for each disease (Doos, Roberts, Corp, & Kadam, 2014). The separate treatment guidelines for single diseases do not consider the effect of comorbidity on increasing polypharmacy (Mannucci et al., 2014).

Also, people with complex medical situations require treatment from different specialists. The lack of integrated care among these professionals in the continuity of patient care increases the chances of polypharmacy and its associated risks (Calderón-Larrañaga et al., 2012). For people with multiple comorbidities, problems arise when there are multiple drug interactions or when it is impossible to comply with the multiple treatment regimens. The literature suggests that the chances of an undesirable combination of drugs and adverse drug reactions increases with an increase in the number of medications (O'Dwyer, McCallion, McCarron, & Henman, 2018).

A recent study in Japan tried to identify the pattern of multiple comorbid conditions that occur in the population and investigate the different effects of the patterns on polypharmacy and dosage frequency.

The authors were able to identify the patterns of diseases in the study population and show the synergistic effect of these patterns on polypharmacy and increase in dosage frequency (Aoki, Yamamoto, Ikenoue, Onishi, & Fukuhara, 2018). The study suggests that with increased disease is associated with increased medications used. As a result of the lack of clear guidance for health care professionals on the best approach to treat patients with multiple comorbid conditions optimally, health care providers need to consider the potential burden of multiple medication use when providing support to patients and prioritizing their management strategies.

The purpose of treating HIV infection and other comorbid diseases is to prolong survival, manage the symptoms of the disease, prevent opportunistic infection, and improve the overall quality of life. To achieve this purpose, health care providers need to collaborate. Pharmacists should work closely with clinicians to ensure medication safety. There is a need for the pharmacist to communicate with the patients to identify adverse reactions, drug interactions, and address problems with medication adherence. Medication therapy management provides an opportunity for pharmacists to provide adequate pharmaceutical care to HIV patients.

2.5 Medication therapy management

Medication therapy management (MTM) is a pharmacist-led intervention for patients to optimize therapeutic outcomes. Pharmacists are one of the most reachable health care providers. Patients with chronic disease or terminal infectious disease tend to visit the pharmacy more often than the average patient. Pharmacists are better positioned to help manage medication regimens. In recent years, pharmacists have been providing patient-centered services in different settings to improve therapeutic outcomes.

Medication therapy management (MTM) is one of the interventions of pharmacists in managing medication regimens (Viswanathan et al., 2015). MTM services allow patients to consult pharmacists who examine the drug therapy needs of the patients and help to prevent, identify, and resolve any drug therapy problems (Detoni et al., 2017).

2.5.1 Components of medication therapy management

MTM has five core components: (1) Medication therapy review, (2) personal medication record, (3) medication-related action plan, (4) Intervention or referral and (5) documentation and follow-up (Byrd, Hardnett, et al., 2019)

Medication therapy review

Medication therapy review is the first step in the MTM process. It is a systematic process where the pharmacist examines the medication regimen of patients for indication, effectiveness, safety, and adherence. It may include the review of the patient's response to treatment and the appropriateness of each medication. The pharmacist examines if the patient is using the proper dose of the drug. The pharmacists also examine if the drugs are used for the appropriate clinical indication.

There are two types of medication therapy reviews 1.) Comprehensive medication review 2.) Targeted medication review. The comprehensive medication review (CMR) involves the pharmacist examining all the patient's medications and health conditions for appropriateness, proper dosing, and response to treatment. While the targeted medication review (TMR) focuses on the review of specific medications used by a patient for some medical conditions and not all the medications taken by a patient.

Personal medication record

After carefully reviewing the patient's medication, the pharmacist then compiles a comprehensive record of all the current and appropriate medications to be taken by the patient. A copy of this record is given to the patient for personal use.

Medication-related action plan

A medication-related action plan (MAP) is a document given to the patient by the pharmacist to track their progress in self-management. The MAP contains a list of actions for the patient in taking their medications and monitoring their treatment response.

Intervention or referral

Some patients with medication-related problems may require medical intervention or a referral after consulting with the pharmacist. When the patient's needs are beyond the pharmacist's expertise or the scope of his practice, the pharmacist refers the patient to a clinic provider.

Documentation and follow-up

Documentation and follow-up are the final steps of an MTM program. At this stage of the consultation, the pharmacist documents the services provided to the patient and schedules a follow-up visit as needed (Byrd, Hardnett, et al., 2019).

2.5.2 MTM in the general population

Studies have demonstrated the ability of pharmacist-provided medication therapy management services to increase medication adherence, improve health outcomes, and reduce health care costs in chronic diseases such as diabetes and hypertension. A pre-post cohort study assessing the impact of pharmaceutical care services in people with diabetes showed that there was a significant improvement in mean HbA1c concentration (Cranor, Bunting, & Christensen, 2003). The study reported an increase in self-monitoring of blood glucose post-study and a reduction in the overall cost of care.

Similarly, a randomized control trial in 14 community pharmacies also evaluated the effect of the intervention of community pharmacists in managing patients with hypertension. The pharmacist offered services such as cardiovascular risk reduction, and counseling, and referral to the primary care provider

for further management when necessary. The study showed that the group with pharmacist-led interventions had a greater reduction in systolic blood pressure at six months when compared with the control group (McLean et al., 2008).

Another study in non-HIV patients showed that medication reviews by pharmacists are beneficial for medication reconciliation. A study conducted in the transition of care in five elderly nursing homes with 750 patients partnered with medical providers and pharmacists to reconcile their medications. The pharmacists obtained electronic health records, pharmacy records, and a brown bag review of the patients' medications. They did a reconciliation of the health records, and the medications used by the participants. They were able to identify medication errors such as inaccurate dosing, medication omission. The study found a positive association between polypharmacy and the presence of medication errors (Koprivnik, Albiñana-Pérez, López-Sandomingo, Taboada-López, & Rodríguez-Penín, 2020). The impact of such interventions has been reported in improving the health outcomes of other chronic diseases. Studies have shown that medication therapy management improves medication appropriateness, adherence, health care cost, and the odds of hospitalization (Brummel, Soliman, Carlson, & de Oliveira, 2013; Viswanathan et al., 2015). There is, however, limited literature on the effect of comprehensive medication therapy management on polypharmacy in people with HIV/AIDS.

2.5.2 MTM in people living with HIV/AIDS

As discussed earlier, MTM programs have been useful in resolving medication-related problems and optimizing clinical outcomes in other chronic diseases. Patients with HIV/AIDS should benefit more from MTM services as they often take multiple medications and are usually under the care of multiple specialists. However, there is limited literature on the effectiveness of pharmacist-provided MTM services on HIV/AIDS. Some studies have described the effect of pharmacists' intervention in managing complex medication regimens. Although these interventions did not include the details of MTM practice, their

effects are worthy of mention. One of the studies was a medical chart review that compared 80 HIV patients who attended a pharmacist-led medication adherence clinic and those who did not attend the clinic. The study showed an improvement in medication adherence (measured by refilling of prescriptions on average every 31 days versus 50 days) and a significantly higher reduction in viral load at 6 months and 12 months in people who attended one educational session with the pharmacist (Cantwell-McNelis & James, 2002). The pharmacists in this study only provided education and counseling on adherence for patients beginning therapy and those who had issues with adherence. The pharmacists only addressed issues related to ART and did not consider the use of other drugs. Therefore, they did not evaluate the effect of the program on polypharmacy

A similar study among 30 AIDS patients and 4 HIV patients evaluated the impact of a drug optimization clinic pharmacist's interventions on the virologic and immunologic responses, and the rate of adverse events in HIV/AIDS patients. The pharmacists' intervention provided includes patient education, the addition of a medication regimen, adjustment of medication dose, discontinuation of medication, and interpretation of the viral test. The study reported a mean increase in CD4 count from baseline level by 54 cells/mm^3 and a mean reduction in viral load by 1.02 $\log_{10}$ copies/ml as well as a decrease in drug-related toxicity (March et al., 2007). Grossberg et al. used pharmacy records to show that there is a correlation between improved adherence and reduced viral load. The study showed that for each 10% increase in adherence rate, there was a decrease in viral load by 0.12 $\log_{10}$ copies per ml (Grossberg & Gross, 2007).

A large-scale cohort study on 7,018 HIV/AIDS patients evaluated the effect of an MTM program comparing 1,353 patients who received MTM services from 10 pilot pharmacies with 5,665 patients who received medications at 2,103 other pharmacies. The study reported improved medication adherence, reduced excess medication refills, reduced contraindicated regimen, decreased change in medication regimen strategy. The total medication cost for each patient was, however, higher in the pilot pharmacies when compared to the other pharmacies (Hirsch et al., 2009). This study did not evaluate the effect of

MTM on HIV outcomes such as viral load and CD4 counts; neither did it assess the effect of MTM programs on polypharmacy.

2.5.3 Conclusion and gaps in Knowledge about MTM programs and polypharmacy in PLWHA

Pharmacist-led interventions such as medication therapy management (MTM) have been useful in resolving medication-related problems and optimizing clinical outcomes. Studies in HIV patients have shown that MTM has the benefits of improving medication adherence, reducing contraindicated therapy, preventing excess medication refills for ART and remaining on a single type of ART regimen (Cantwell-McNelis & James, 2002; Hirsch et al., 2011; Hirsch et al., 2009; March et al., 2007). These studies only focused on ART and did not include other medicines used by PLWHA that may contribute to polypharmacy. From the review of literature, the effectiveness of pharmacist-provided MTM services in reducing polypharmacy in HIV/AIDs patients has not been well studied.

It is expected that MTM services should enable the identification and reduction of polypharmacy. MTM services for HIV patients should involve the evaluation of the ability of the patients to adhere to medications. It should identify and manage adverse drug reactions, tailor ART regimens to individual needs, counseling when there is overuse or underuse of medications, refill reminder services and referral for other medical services when needed (Hirsch et al., 2011).

Also, drugs in fixed-dose combinations might complicate medication reviews during MTM services if the product name is not provided to the pharmacist. Considering only the number of pills and ignoring the polyactive substances in combination drugs, increases the likelihood of missing the possible adverse effects that may occur when reviewing their medications during an MTM intervention. Having an improved understanding of the polyactive substances in medicines used by HIV patients with complex medication regimens will promote effective drug utilization.

Finally, researchers have linked pharmacist interventions to improved viral suppression and CD4 counts in people living with HIV/AIDS, but no studies have examined the role of polypharmacy in achieving improved HIV outcomes.

CHAPTER 3: METHODS

3.1 Overview

The long-term goal of this research is to study ways to ensure the efficient use of medications among people living with HIV/AIDS (PLWHA) and ultimately decrease the risks associated with unnecessary excessive medication use. The purpose of this study was to evaluate the impact of medication therapy management on polypharmacy in people with HIV/AIDS. The objective was achieved through the following specific aims.

1. **Determine the difference between the pill count and the number of polyactive substances in medicines of PLWHA**.

Secondary data analysis using the data obtained from the patient-centered HIV care model study was conducted to determine if there was a significant difference between the number of pills and the number of polyactive substances in medications used by people with HIV/AIDS.

2. **Determine the relationship between polypharmacy as defined by the number of polyactive substances in medications used by PLWHA at the beginning and at the end of an MTM program and the factors that may affect the change in the number of polyactive substance.** Secondary data analysis of the patient-centered HIV care model study was conducted to determine if the medication therapy management program had an impact on the number of polyactive substances in medications used by PLWHA throughout the study. The possible factors that may affect the change in the number of polyactive substances were identified.
3. **Examine the relationship between the number of polyactive substances and the changes in HIV-related outcomes such as CD4 count and viral load suppression and the magnitude of improvement of other chronic disease outcomes such as (HbA1c and fasting plasma glucose in diabetes and systolic blood pressure in hypertension) during an MTM program.** Secondary data analysis of the Patient-centered HIV care model study was conducted to determine if the viral suppression and increase in CD4 count reported in this study are related to a change in the number of polyactive substances.

3.2 Data source and project description of the CDC study

The data for this project was obtained from a Patient-Centered HIV Care Model (PCHCM) study. The goal of the project was to determine if active referrals between community-based pharmacists and clinical providers can provide more patient-centered care for HIV patients and lead to an improvement in HIV care and treatment. The PCHCM was a collaboration project between the Center for Disease Control (CDC), Walgreens Co. pharmacy, and the University of North Texas Health Science Center. The details

of the recruitment and site have been described in detail in the article by Dr. Byrd (Byrd, Hardnett, et al., 2019) but will be reiterated here to describe the process of data collection clearly.

3.2.1 Institutional Review Board approval

The information collected for this project was de-identified. The CDC determined that the PCHCM constituted a public health program activity and not a research activity. Likewise, the Institutional Review Board of the University of North Texas Health Science Center classified the project as an exempt status. Data abstracted from this project for the secondary data analysis did not contain any variable that could identify the patient.

3.2.2 Project sites

The study took place in 10 project sites, which consisted of 1 to 2 pharmacies that partnered with a medical clinic across 8 states in the United States. The project sites were located in Albany, GA; Chicago, IL; Fort Lauderdale, FL; Miami FL; Kansas City, MO; St. Louis, MO; New York, NY; Palm Springs, CA; Philadelphia, PA; and Washington, D.C. The clinics used for the project were identified based on the Clinic's HIV population after reviewing the Health Resources and Services Administration's Uniform Data System and the Ryan White HIV/AIDS Program Services report. Every identified clinic was matched with a project pharmacy nearby. These pharmacies were community-based HIV specialized retail pharmacies of a national pharmacy chain. The pharmacies had appropriate HIV medications and had pharmacists who provided hands-on patient care and adherence support. The pharmacists and pharmacist technicians were all previously trained on the treatment of HIV, how to prevent stigma, and how to ensure cultural competency. However, regular and current educational updates on HIV/AIDS were provided to the pharmacists (Byrd, Hardnett, et al., 2019).

3.2.3 Population

Seven hundred and Sixty-five study participants living with HIV/AIDS were recruited from the project clinics. Participants were eligible if they were 18 or older at the time of enrollment; they were on ART or planned to start ART. Other eligibility criteria were the willingness to visit the clinic every 6 months and to have an initial and quarterly MTM visits. Participants must also be willing and able to use the project pharmacies to get their prescribed medications. The exclusion criteria were residing in a long-term care facility, use of an investigational study drug, clinical trial participation, presence of a comorbid condition, or the use of an active substance that could interfere with the compliance of project requirements (Byrd, Hardnett, et al., 2019).

3.2.4 Structure of the Patient-Centered HIV Care Model

The structure of PCHCM was designed to improve upon the MTM project by including the medical providers. The MTM differed from the PCHCM in that the medical providers shared information about the patients with the pharmacy and vice versa. The information-sharing was to enable the pharmacist to conduct a more detailed MTM by taking into consideration the participants' medical history. The information shared included the patient's current and previous medical conditions, CD4 test results, HIV viral load, liver function test, serum creatinine, other laboratory test results, current and discontinued medications, drug allergies, immunizations, history of alcohol, tobacco use, and substance abuse.

The study participants were required to have quarterly follow-up visits with the community pharmacists. The project pharmacists also helped the patients to ensure continuous adherence to treatment by proactively monitoring their medication refills. The pharmacists monitored their medical history and laboratory test results to assess their response to treatment. The pharmacist also identified any potential drug-related adverse events and any problems with their medical history or laboratory tests. They collaborated with the partnered clinics to make recommendations and discussed the intervention strategies

or the potential action plan for problems identified during the MTM sessions. The pharmacists, medical providers, and patients then worked together to implement the medication-related action plan.

3.2.5 Project procedures

The prospective patients were approached by the clinic and pharmacy staff to explain the voluntary nature of the project and to determine their willingness to participate. There was no requirement for written informed consent. One thousand one hundred and fourteen persons with HIV were approached for the project. Seven hundred and ninety-eight persons agreed to participate. Patients who agreed to participate in the PCHCM project were referred to the partnering pharmacist to schedule an initial comprehensive medication review (CMR). Only 765 of those who agreed to participate had an initial Comprehensive medication review. See figure 6 for the flow diagram for inclusion in data analysis for each aim.

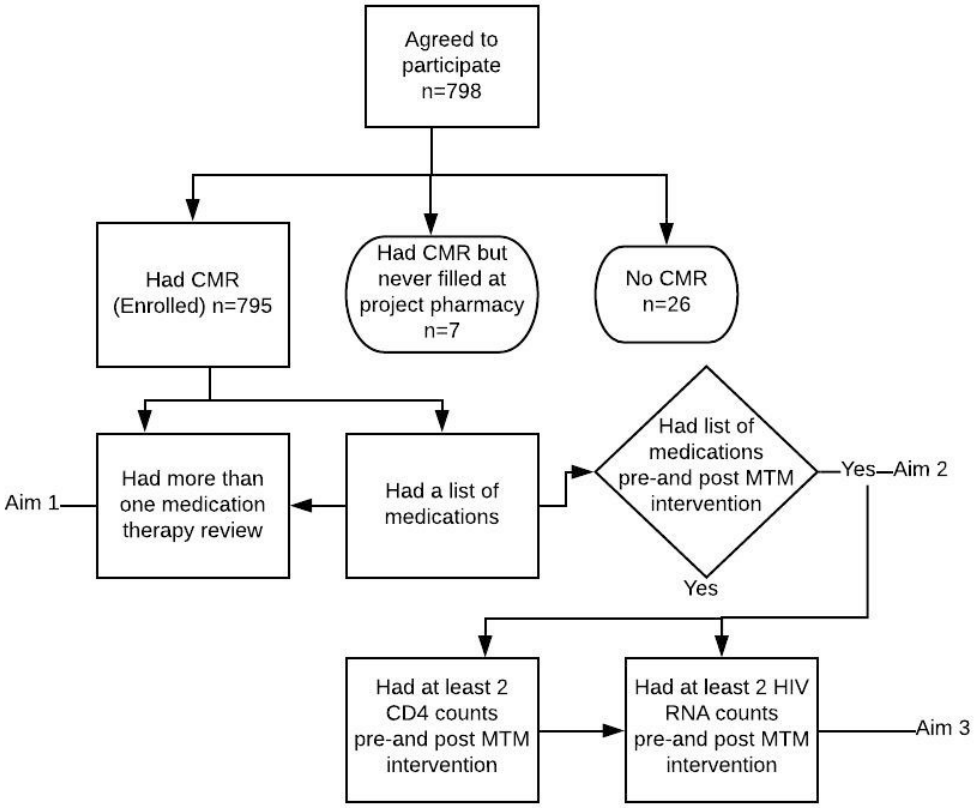

Figure 6 Flow diagram for inclusion into data analysis for each aim

The pharmacists were given access to 2 years of the participants' medical history before the first CMR visit. This medical history was updated every quarter to ensure that the pharmacists had the complete medical details of the participants.

There were also follow-up visits, which were conducted in-person or by phone. At the follow-up visits, the pharmacist reviews all the HIV-related medications and drug-related problems the patients may be experiencing. The pharmacists also reviewed the Non-HIV medications and other medical conditions the patients had when it was clinically necessary. Pharmacist support was made available as frequently as

needed. Participants could consult with the community pharmacist when they refill their monthly drug prescriptions.

The pharmacists then forwarded consultation notes to the clinic. When necessary, the pharmacist made a request to the clinician that specific medications be started or discontinued. The pharmacist may also recommend a change in the medication dosage. Sometimes additional laboratory tests may be required. Whenever the pharmacist identified a medical or medication-related problem, a recommendation was made with the clinic provider, and a plan was developed to address the problem. All the details of the CMRs and follow-up visits and laboratory results related to the project were recorded in a data collection form. All participants received at least one year of MTM services. Although the primary goal of the PCHCM was to improve HIV care. We expect that the program would have a positive effect on polypharmacy. Hence the need to evaluate the effect of the program on the number of medications used by PLWHA.

3.3 Secondary Data

The data from the PCHCM program described above were utilized for this study. The data for this study was in two parts. The initial data had records of the patients' unique identifier, the enrollment date, physical profile, age, gender, race/ethnicity, education status, insurance, employment status, the details of the first visit, blood pressure, medication records, indication, and vaccination records. It also had laboratory results, which include- liver function tests, renal tests, blood glucose test, lipid profile, CD4 count, and viral load results. It also had the comprehensive medical review dates and the targeted medical review dates.

The second part of the data is combined data of quarterly visit reports from the study participants. It has patient information for three different quarters of the study with updated information about the patients on similar variables as the initial data. It also has an updated report on HIV RNA count, CD4

count. The data also has a more comprehensive report of the medication changes, the reasons for the change in medication, medication reaction, and allergy. Other variables in the data include further lab test results, including bilirubin, urinalysis, chemistry panel, hepatitis screening, syphilis screening. Only the needed variables in the data were abstracted for this study. For aim 1, only the initial data was used while in aim 2, and aim 3, both the initial and the follow-up data, were used for the analysis.

3.3.1 Data preparation

The first step in this secondary data analysis was to develop the analytic data set. This was done by examining the initial and follow-up data to determine the variables for answering the research question.

3.3.1.1 Data preparation for Aim 1

The list of all current medications used by the 765 study subjects at the beginning of the PCHCM study was obtained from the initial data. A total number of 10,917 medication entries were obtained from the 765 people living with HIV. The sample data were cleaned to remove all extraneous variables. Medication entries with spelling errors were corrected. All medications with brand names were converted to their generic forms to ensure consistency and to avoid duplicate entries. All duplicate medication entries per individual were deleted. The resulting medication list contained a total of 6,606 medication entries for all the participants with 557 different medications. The list of changes made to some of the medications is in the supplementary list in appendix 2 (Table 10).

The polyactive substances in each medication were determined by checking for the pharmacologically active ingredients in each medication from the A-Z drug database online. The data source uses IBM Watson Micromedex and Wolters Kluwer^{TM}, as databases, which are the largest online reference database for drug information. The list of the medication changes from brand name to generic

name and the corresponding polyactive substances are shown in Table 2 in the appendix. The drug classes were determined by using the Anatomical Therapeutic Classification system Table 5.

All the pills taken by each study participant were summed to get the total pill count. The sum of pharmacologically active ingredients (polyactive substances) in the medications used was also determined to get the polyactive substance count per person. The demographic variables, age, gender, race/ethnicity, education status, insurance, and employment status were then recoded into categories for the analysis (Table 1).

3.3.1.2 Data preparation for Aim 2

The medications used at the beginning of the study were obtained from the initial data already described in aim 1. While medications used by participants during the study and at the end, was obtained from the combined follow-up data. A total number of 22,230 medication entries were collected from the follow-up data. These medications included all current HIV medications, all opportunistic infection medications, non-HIV medications, all current medications, and over the counter medications. The data were cleaned to remove extraneous entries and correct errors in the medication names.

After cleaning the data, there were 15,901 medication entries with 600 unique medications. A similar process with aim 1 was used to determine the polyactive substances in the follow-up data. Table 3 shows the brand names and generic names of the medications with more than one polyactive substance in the follow-up data. The data were sorted by dates to determine the medications used by each study participant at the last visit for medication therapy management. The total number of polyactive substances in the medications used by each study participant at their latest MTM visit was determined.

The number of the comprehensive and targeted medication reviews attended by each study participant was obtained. For aim 2, the final data for analysis consists of merged data for the polyactive substances used at the beginning and the end of the MTM intervention, the demographic variables, the

total number of medication review visits, and the number of months between the medication entries. The data had repeated measures for each study subject over time.

3.3.1.3 Data preparation for Aim 3

The data for the polyactive substances from the second aim was used in aim 3 but we were also interested in the HIV-related outcomes as the outcome variable. Data for the CD4 counts and CD4 dates, enrollment dates were obtained from the initial data for the beginning of the study. The data were cleaned and converted to consistent formats for ease of analysis. Seven hundred and sixty-five participants had an enrollment date, and 760 of them had at least a CD4 count. Seven of them did not have a date with their CD4 count, and 2 of them had a negative CD4 count, 1 had double CD4 entries with the same date, so they were excluded from the analysis. Seven hundred and fifty participants had an initial CD4 count with a date. The CD4 counts were sorted by the CD4 dates, and the most recent CD4 counts before the enrolment date were obtained. Seven hundred and fifty-one participants had a CD4 count before the enrolment and were included in the analysis. Data for the CD4 count, and CD4 dates, for the end of the study, were obtained from the follow-up data. Only the CD4 counts obtained at the last visit dates were considered. Seven hundred and twenty-one participants had the latest CD4 counts with CD4 dates.

HIV RNA count and HIV RNA dates and enrollment dates were obtained from the initial data to determine the viral load at the beginning of the study. A total of 736 participants had an HIV RNA count with a date before the enrolment date. The last HIV RNA on or before the first comprehensive medication review visit date was used as the initial HIV RNA count. The data were cleaned and converted to consistent formats for the analysis. Data for the HIV RNA count, and HIV RNA dates for the end of the study were obtained from the follow-up data. The data were cleaned to remove all extraneous variables, missing values, and duplicates. For this analysis, 719 participants had the latest HIV RNA count and HIV RNA dates.

The data from the beginning and the end of the study were merged in a longitudinal format. The time difference in days between the first and the CD4 dates and HIV dates was determined and included in the analysis.

3.3.2 Inclusion and exclusion criteria

Inclusion Criteria

For aim 1, all participants with medication records were included. For aim 2, all participants with medication records pre- and post- MTM intervention. For aim 3, participants included in aim 2 who had at least 2 records of viral load (HIV RNA count) and CD4 counts with dates pre-post-MTM intervention.

Exclusion Criteria

For aim 3, participants with no date entries with their CD4 count and HIV RNA count were excluded from the analysis.

3.3.3 Included and excluded variables

Included variables

The medications included current ART medications, current opportunistic infection medications, other current medications, including over the counter medications.

Excluded variables

The entries excluded are diagnostic supplies such as glucose test strips, lancets, needles, syringes, blood pressure monitors, and nebulizers from the analysis. Other entries that were excluded are compression stockings, Epsom salt, condom with nonoxynol-9, fps formula, knee-high stockings, catheters, shampoos, mouth wash, and vaccines, multivitamins, flaxseed oil, fish oil, Metamucil, and psyllium were deleted because they are supplements with varying pharmacologically active ingredients. Topical medications were also removed from the data.

3.4 Aim 1 methods

In aim one, we were investigating if there is a difference between pill counts and polyactive substances in medications used by people living with HIV/AIDS in the PCHCM study.

3.4.1 Variables for Aim 1

The outcome variable was the number of pills, and the number of polyactive substances used by the study participant at the start of the study. The number of pills was determined as continuous count of the number of medications taken by each study subject.

The number of polyactive substances (pharmacologically active substances) in the medications used by the participants. Polyactive substance was also analyzed as a continuous variable.

The covariates were the demographic variables which included annual income, type of health insurance, gender, race/ethnicity, age, and education. Demographic variables with multiple missing values were recoded as unknown/missing. Age, which was a continuous variable, was categorized for the analysis (Table 1) in the appendix shows how the demographic variables were recoded. Recoding these variables was based on previous studies published by authors using the data for this study (Byrd, Hardnett, et al., 2019; Byrd, Hou, et al., 2019).

3.4.2 Statistical Analysis

Descriptive statistics

Descriptive analysis procedures were used to determine the mean and frequencies and to examine the distribution of each of the demographic variables. Descriptive statistics were computed for each variable after re-categorization using frequencies and percentages. The mean, standard deviation, and

95% confidence intervals (CI) of the number of pills and polyactive substances used by the study participants were also determined. Statistical analysis was performed using SAS software version 9.4.

To answer specific aim 1, a paired sample t-test was used to determine if there was a significant average change between polyactive substances count and the pill count in medications. Statistical significance was set at a P-value < 0.05. To find the factors that may be associated with the difference between pills and polyactive substances- The difference between the polyactive substance count and pill count was determined, and a linear regression analysis was done to identify potential covariates. The linear regression model was fitted with the outcome variable (The difference in pill and polyactive substance count) and covariates (individual demographic variables). All categorical predictors were re-coded as dummy variables for this analysis.

3.5 Aim 2 methods

In aim 2, we are investigating the effect of the medication therapy management intervention program on the change in the number of polyactive substances in medications used by people living with HIV pre-post MTM intervention and the factors that may affect the change in the number of polyactive substances.

We were trying to answer the research question that among adults with HIV/AIDS who had medication therapy management in the PCHCM study, was there a change in the number of polyactive substances used pre-post MTM intervention and what are the factors that can affect the change.

3.5.1 Variables for Aim 2

The outcome variable of interest was the change in the number of polyactive substances from the beginning to the end of the study. Which was analyzed as a continuous variable between time.

Covariates: Some of the variables that may affect the change in the number of polyactive substances in medications used by the study participants were factored into the analysis. These include the demographic variable described in Aim 1. Also, the duration between the first CMR and the last CMR visit expressed in months and was analyzed as a continuous variable.

Time, which represents the time point at which the first and last medication measurement was taken, was categorized as 0 or 1 and was included in the analysis.

Also, the total number of comprehensive medication reviews and targeted medication reviews attended by each study participant was determined and included in the analysis.

3.5.2 Statistical Analysis for Aim 2

The mean and frequency of polyactive substances in medications used by the study participants at the beginning and end of the study were determined (Pre-and post-intervention).

The generalized mixed-effects regression model was used to analyze the change in the number of polyactive substances in medications used by the study participants pre- and post-medication therapy management intervention. The unique identifier number (Person_ID) was included as a random subject effect in the regression model to account for the influence of subjects on their repeated observation and to explain the correlational structure of the longitudinal data.

The total number of polyactive substances pre- and post- MTM intervention for all participants were compared. The covariates included in the analysis are: the number of months in the study, the time point between medication measurements 0 for baseline and 1 for the endpoint, demographic variables, and the number of comprehensive medication reviews and targeted medication reviews were included in the analysis.

3.6 Aim 3 methods

In aim 3, we were investigating the relationship between the change in HIV outcomes and the change in polyactive substances in medications used from the beginning to the end of the study. For aim 3, the analysis is in two parts because we are analyzing the relationship between two HIV related outcomes CD4 counts and HIV RNA count and the change in polyactive substance during an MTM intervention.

3.6.1 Variables for Aim 3

The outcome of interest was in two parts: 1. The change in the CD4 count at the beginning and end of the study. The CD4 count was analyzed as a continuous variable and as a categorical variable. CD4 count was categorized as less than 200 cells/mm^3 and greater than or equal 200 cells/mm^3 based on the differentiation between HIV and AIDS.

2. The change in the HIV RNA count at the beginning and at the end of the study. HIV RNA count was analyzed as a categorical variable. It was coded as less than 200 copies/ml and greater than or equal to 200 copies/ml based on the differentiation of those with viral suppression or not.

The covariates were the change in the number of polyactive substances pre-post MTM intervention. Other covariates considered in the analysis were the number of days between the first and the last CD4 and HIV measurements. Also, the time between the first and last medication measurements was included in the analysis with the demographic variables used in aim one above.

3.6.2 Statistical analysis

3.6.2.1 First part of aim 3- CD4 counts

The CD4 count was also categorized as ≥ 200 and <200 to determine the improvement in CD4 count throughout the study. A cutoff of 200 was used because a count of <200 is used to differentiate

those with Acquired Immune Deficiency Syndrome (AIDS) from those with HIV. A CD4 count of ≥ 200 cells/mm^3 was used to denote an improvement in CD4 count. Generalized estimating equation with a logit link function using a log-binomial regression link was used to model the relationship between the change in CD4 count categories and the change in the number of polyactive substances pre-and post-implementation of the PCHCM program. Other variables included in the analysis are time, and time by polyactive substance interaction term. The analysis also sought to identify the demographic factors that predicted a change in CD4 count categories during the program. The demographic predictors in the analysis - age, race/ethnicity, insurance, income, education, housing status. Statistical significance was set at 0.05. The equation for the relationship is $Y\ (CD4\ improvement) = \beta_0 + \beta_1\ (Polyactive\ Substance) + \beta_2\ (time) + \beta_3\ (Polyactive\ Substance*time) + \beta_4$ Covariates……+ υ

3.6.2.2 Second part of Aim 3- HIV RNA count

HIV RNA count was then categorized to calculate the proportion of people who were virally suppressed pre- and post-model intervention. Viral suppression was defined as those who had a viral load of ≤ 200 HIV RNA copies/ml at the first and the last test in the study period. Those who had a viral load of > 200 HIV RNA copies/ml were considered not to be virally suppressed. The cutoff value of < 200 copies/mL was based on the Department of Health and Human Services (DHHS) recommended definition of virologic failure. The proportion of persons who had HIV viral suppression was modeled using log-binomial regression. Repeated measures were accounted for by using the generalized estimating equation with a logit link function and binomial distribution. A comparison of HIV viral suppression pre- and post-MTM intervention for the study population was used as the outcome variable. While the number of polyactive substances pre and post-study was the main predictor, time at the beginning and end of the study as well as a polyactive substance by time interaction term was also included as predictors in the study. The analysis also sought to identify the demographic factors that predicted HIV viral suppression.

Additional predictors that were added included the number of Comprehensive medication reviews and targeted medications per participant. The equation for the relationship is $Y\ (Viral\ suppression) = \beta_0 + \beta_1\ (Polyactive\ Substance) + \beta_2\ (time) + \beta_3\ (Polyactive\ Substance*time) + \beta_4$ Covariates……$+ \upsilon$

CHAPTER 4 RESULTS

4.1 Overview

The goal of this study was to understand the impact of medication therapy management on polypharmacy in people living with HIV by using polyactive substances in medications used by the study participants as a measure. The results of this dissertation are presented in three sections based on the three aims of the study. First, the analysis of aim 1, which examined the difference between the pill counts and polyactive substances in medications used by people living with HIV/AIDS. Second, the result of the analysis of the change in the number of polyactive substances in medications used by PLWHA at the beginning and at the end of a modified medication therapy management intervention are presented. Third, the analysis of the relationship between HIV-related outcomes and the change in the number of polyactive substances in PLWHA at the beginning and the end of a modified medication therapy management intervention are presented.

4.2 Aim 1 results

4.2.1 Description of the sample.

The final sample from the CDC dataset comprised of 765 people living with HIV/AIDS (Table 4), with the majority being men (73%) the remaining were women (25%) and transgender (2%). Among the study participants, the number of people with HIV was 628 (82%), while 138 (18%) had AIDS at the beginning of the study. The demographic characteristics of the study participants indicated that the majority were black non-Hispanics, had at least a high school education, earned less than $15000 per annum, employed or with multiple jobs, and had insurance coverage. Almost half of the study participants were aged 50 years or older, with the youngest being 18 years and the oldest being 83 years old. The total number of unique medications used by all the participants was 562. The minimum number of pills used by a person in the study was one while the maximum number of pills was 26, as shown in Figure 6.

The minimum number of polyactive substances in the medications used by the participants was two, while the maximum was 31 polyactive substances Figure 7. There are about 100 different classes of drugs used by the study participants. The drug classes with the highest frequencies include antihypertensives, antibiotics, antiretrovirals, analgesics, vitamins, hypoglycemic agents, corticosteroids, anti-inflammatory drugs, antidepressants, antifungals, antihistamines, antivirals, lipid-lowering drugs, anticonvulsants, and antipsychotic drugs. The details of the classes of drugs and their frequencies can be found in Table 8 in the appendix.

4.2.2 Difference between pill count and polyactive substance in medications used by PLWHA

The mean number of pills used by participants in the study was 8, with a standard deviation of 4.51. The mean number of polyactive substances in medications was 11, with a standard deviation of 4.84. Using the pill count, the percentage of the study participants who used five or more drugs was 78%. In contrast, while the percentage of study participants with five or more polyactive substances was 92%.

4.2.2.1 Result of Paired T-test analysis

The paired sample T-test showed that there is a significant difference between the number of polyactive substances and the pill count. The average difference between the polyactive substance count and the pill count is about 2.15, with a 95% confidence interval of [2.05 - 2.24]. The test statistic is 44.71, with a p-value of 0.001.

4.2.2.2 Result of Simple linear regression

The regression model examining the relationship between the difference in polyactive substance and pill count and the demographic factors adjusted for race/ethnicity, age, insurance coverage, education level, employment and found no statistically significant relationship except for those who used private insurance Table 6

4.3 Aim 2 results

4.3.1 Description of the sample

At the beginning of the study, there were records of the medications used by 765 participants, while only 736 participants had records of the medications used at their last MTM visit. Twenty-nine participants were lost to follow-up either because they did not attend more than one MTM session, died, or had no dates with their medication records. The proportion of people with > five polyactive substances reduced from about 92% pre-MTM intervention to about 85% post-MTM intervention.

The months and the number of medication therapy reviews were also factored into the analysis. The number of months between medication record entries ranges from 1 month to 34, months with an average of 14 months. The number of comprehensive medication reviews and targeted medication reviews range between 1 and 9 visits with the majority of participants having four visits. See Figure 9.

4.3.2 The change in polyactive substances in medications used by PLWHA during the study

At the beginning of the study, the average number of polyactive substances in medications used by the participants was 10, while at the end of the study, the average number of polyactive substance was 8. The maximum number of polyactive substances reduced from 35 pre-intervention to 18 post-intervention. The difference between the number of polyactive substances at the beginning and the end of the study ranged from -9 to 25 polyactive substances as shown in Figure 10.

The result of the mixed model regression analysis showed that there was a significant change in the number of polyactive substances in medications used by the study participants over time. It showed that as time changes in the intervention, the number of polyactive substances decreased by approximately

3. The result in (Table 7) shows the change in polyactive substances pre- and-post model intervention after adjusting for demographic predictors.

The number of polyactive substances in medications used by study participants reduced by an average of 3 from pre- to post- medication therapy management intervention. The change in polyactive substance was significant among age group categories, blacks and Hispanics when compared to whites, people with Medicare, and multiple insurances when compared to those with private insurance and employment status.

4.4 Aim 3 results

4.4.1 Part 1 Aim 3: Relationship between CD4 count and polyactive substances

4.4.1.1 Description of the CD4 counts as a marker of HIV outcome

At the start of the study, the CD4 counts of the participants range from 1 to 4730 cells/mm^3, with an average of 524 cells/mm^3 ± 366.3496634. Of the 750 people in the study, 18% have CD4 counts less than 200 cells/mm^3 which is the definition of AIDS. While 82% of the study population have CD4 counts of ≥ 200 cells/ mm^3 HIV only.

At the end of the study, the CD4 counts of the participants range from 5 cells/mm^3 to 2120 copies/ml with an average of 585 cells/mm^3 ± 338 cells/mm^3.

Only 704 participants with a final CD4 count measurement with a date. 87% had HIV, while 13% had AIDS. The number of days between the first and last measurement of the CD4 count was also factored into the analysis. An average of 441 days lapsed between the baseline CD4 count and the final CD4 counts' measurement. The number of days between CD4 measurements ranges from 1 to 1199 days.

4.4.1.2 Result of generalized estimating equation analysis

The relationship between the change in CD4 count categories (<200 cells/mm^3 and ≥200) cells/mm^3) and the change in polyactive substances over time was determined.

The results show that as polyactive substances go up over time during MTM intervention, there is an 8% decrease in the chances of having a CD4 count ≥200 cells/mm^3. Odds Ratio = 0.9206 {CI = 0.8508 - 0.9856} with a p-value of 0.0175. This relationship was significant after adjusting for days between CD4 count measurements, the number of comprehensive and targeted medication reviews, age, race/ethnicity, insurance, income, education, and housing status. Employment status was not included in the analysis because it did not fit into the model. When holding other variables equal, MTM intervention as a measure of time was a significant predictor of the change in CD4 count categories (Odds Ratio = 2.7725 {CI= 1.4283- 5.3817} with a p-value = 0.0026). For an increase in time in the MTM intervention, there is 2.77 times higher odds of a subject having a CD4 count ≥200 cells/mm^3 holding other variables constant. Other significant factor associated with improved immunologic status (CD4 count ≥200) cells/mm^3 are black non-Hispanics (Odds Ratio = 0.4107 {CI =0.2273 – 0.7423} with a p-value = 0.0032). Black, non-Hispanics have 60% lesser chance of having a (CD4 count ≥200) compared to white, non-Hispanics when holding all other variables constant. The details of the analysis are shown in (Table 8) in the appendix.

4.4.2 Part 2 of aim 3 result: the relationship between changes in viral load (HIV RNA count) and polyactive substances over time.

4.4.2.1 Description of viral load as a marker of HIV outcome

The viral load of study participants ranges from 0 to 1,295400 copies/ml, with an average of 18266.40 ± 78583.87 copies/ml. Only 732 of the study participants had an HIV RNA reading before the start of the study. The proportions of people who were virally suppressed (HIV RNA <200 copies/mL)

before the program implementation were 74.24% while the percentage of people who were not virally suppressed (HIV RNA >= 200 copies/mL), was 25.76%. At the end of the program implementation, only 719 of the study participants had an HIV RNA count with a date. The viral load ranges from 14 to 2,925582 copies/ml, with an average of 11567 copies/ml ± 117168.41 copies/ml. The proportion of people who were virally suppressed at the end of the study was 87%, while those who were not virally suppressed were about 13%.

Overall, viral suppression improved by about 15%, from 74% pre-implementation to 87% post-implementation (P<.0001).

4.4.2.2 Result of generalized estimating equation analysis

The relationship between the change in viral suppression status denoted by HIV RNA (<200 cells/mm^3= suppressed) and (≥200) cells/mm^3= not suppressed) and the change in polyactive substances over time was determined. The results showed that as polyactive substances go up over time during the MTM intervention, there is a 10% decrease in the chances of being virally suppressed (having HIV RNA<200 cells/mm^3). (Odds Ratio = 0.8926 {CI: 0.8151 - 0.9775} with a p-value of 0.0142).

Independently, MTM intervention which was indicated by time, was also significantly associated with viral suppression (Odds ratio = 6.0977 {CI = 2.6853 – 13.8462}, p-value <0.0001). The number of polyactive substance itself was independently associated with a significant improvement in viral suppression (Odds ratio = 1.0477 {CI = 1.0048 – 1.0926}, p-value = 0.029). For an increase in polyactive substance, a subject is 4.7% more likely to have viral suppression than a subject with a lesser number of polyactive substance when holding all other variables as equal. Other significant predictors of viral suppression were all age categories, and being black, non-Hispanic.

The relationship between the change in viral load and polyactive substances during the MTM intervention was significant after adjusting for days between viral load measurements, the number of

comprehensive and targeted medication reviews, age, race/ethnicity, insurance, income, education, and housing status. Employment status was not included in the analysis because it did not fit into the model. The details of the analysis are shown in Table 9.

CHAPTER 5 DISCUSSION

5.1 Overview

Polypharmacy, which is commonly defined as the concurrent use of five or more medications, is a rising concern among people living with HIV. Besides the use of antiretroviral therapy, which typically requires about three or more HIV medications, many non-HIV medications are given to prevent or treat symptoms, side effects, and comorbid disease. It is estimated that about 15 to 39% of people with HIV are exposed to polypharmacy, and this exposure occurs about a decade earlier than the general population (Guaraldi et al., 2018; Justice et al., 2018; Siefried et al., 2018; Ware et al., 2018). People living with HIV are more susceptible to increased risk from polypharmacy because of medication side effects and decreased medication adherence, which may impair their ability to maintain viral suppression.

Although polypharmacy has been measured as a threshold (five medications) using the pill count, the pharmacologically active ingredient (polyactive substances) in medications must also be considered. Given that most medications for chronic diseases, as well as antiretroviral drugs, come as polypill (a combination of multiple drugs as a single pill), each additional polyactive substance increases the risk for potential adverse events and drug interaction. Therefore, the first aim of this study was based on the premise that using the number of polyactive substances to define polypharmacy may be more accurate for identifying the specific risks of each substance. This dissertation was designed to address this issue by providing a direct comparison between the number of pills and the number of polyactive substances in medications used by PLWHA.

Also, as polypharmacy presents unique management issues in people with HIV, pharmacist led-interventions such as medication therapy management may be useful in addressing polypharmacy in HIV. Medication therapy management with clinician involvement may further help to promote safer and appropriate prescribing as it provides the opportunity for complete medication reconciliation, screening, assessment, and treatment of medication-related issues. This study is based on the premise that medication therapy management is essential to improving the outcomes of care and preventing unwarranted or excessive medication use in people living with HIV/AIDS. Based on an extensive literature review, few researchers have examined the relationship between medication therapy management on polypharmacy in other chronic diseases. However, no one has examined this relationship in HIV patients.

This study was designed to examine the gaps in the literature regarding the impact of a modified medication therapy management program on polypharmacy by using the pharmacologically active ingredients in medications (polyactive substances) as a proxy. Analysis of PCHCM data from 765 adults was used to evaluate three aims:

Aim 1: Determine the difference between the pill count and the number of polyactive substances. in medicines of PLWHA.

Aim 2: Determine the relationship between polypharmacy as defined by the number of polyactive substances in medications used by PLWHA at the beginning and at the end of an MTM program and the factors that may affect the change in the number of polyactive substances.

Aim 3: Examine the relationship between the number of polyactive substances and the changes in HIV-related outcomes such as CD4 count and viral load.

5.2 Description of drug use in the study participants

Due to the arbitrary nature of using cut off points for defining polypharmacy, we tried to refrain from giving a cutoff for polypharmacy in this study. However, it is worthy of note that the number of pills used by the study participants ranges from 1 to 26, while the number of polyactive substances in the medications ranges from 2 to 31. The average number of pills used by the study participants was 8, while the average number of polyactive substances was 11. These are a little lower than the average number of medications used by PLWHA in other studies. Studies have reported an average of 13 or more medications used by HIV patients (Clay, 2004; Ware et al., 2018) but this may vary due to the difference in patient characteristics. Also, both discontinued and new medications might have been counted, but in this study, we counted only the current medications reported at the time of data entry.

Nonetheless, from the number of drugs used per participant in this study, it is evident that almost all the subjects experience polypharmacy if the definition of using multiple drugs simultaneously is applied. It is also clear that certain forms of polypharmacy are inevitable when treating chronic diseases and in people living with HIV/AIDS. This is further evident from the class of drugs used by participants in this study. Drugs for chronic diseases like hypertension and diabetes were among the most prevalent medicines used by participants in this study. Although the analysis done in this study did not include the types of comorbid disease as a variable, the pattern of drug use suggests that a majority of the participants have comorbid diseases, which may likely increase their use of multiple medications simultaneously.

5.3 Pills and polyactive substances

Using the data from the Patient-Centered HIV care Model, this study found that among people with HIV, there is a mean difference of 2 between the number of polyactive substances in medications and the number of pills. The results confirmed the hypothesis that there is a difference between polyactive

substances and pills, which indicates that using the number of polyactive substances in medications may be a better estimate of polypharmacy

There are not many pieces of literature on the use of polyactive substances in measuring polypharmacy. However, the finding in this study is similar to the study comparing the extent of polypharmacy (using the number of drugs) and the number of polyactive ingredients among patients taking cardiovascular medicines (N. Abolhassani & Marques-Vidal, 2018). Other authors were able to show further increase in the prevalence of polypharmacy when using polyactive substances compared to using pills (Nazanin Abolhassani, Castioni, Marques-Vidal, Vollenweider, & Waeber, 2017; Castioni et al., 2017). While these studies only showed an increase in the prevalence of polypharmacy while using pill count and were conducted in cardiovascular settings. This study was able to provide statistical evidence that there is a mean difference between pills and polyactive substance use among people living with HIV/AIDS.

The increase in the prevalence of polypharmacy when using polyactive substances rather than pill count can be attributed to the fact that most chronic diseases and some infectious diseases are commonly treated with fixed-dose combination drugs. A fixed-dose combination drug regimen is considered to be the standard of care for people living with HIV/AIDS. Multiple drugs are combined into single pills to ease the pill burden. In this study, there are at least 95 different medications used by the participants that are combinations of more than one drug. It is, therefore, essential to consider the specific pharmacologically active ingredients in pills when defining polypharmacy.

5.4 The impact of Medication therapy management on polyactive substances in medications used by PLWHA.

The primary purpose of conducting aim II was to determine the effect of medication therapy management intervention on polypharmacy using polyactive substances as a determinant. The results of

the analysis showed that over time in this study, the number of polyactive substances in medications used by PLWHA decreased by about 3. The descriptive analysis of drug use also showed that the average number of polyactive substances reduced from 11 to 8. Also, the maximum number of polyactive substances taken by a participant decreased from 31 to 18. The results indicate that medication therapy management is beneficial in reducing polypharmacy in HIV patients. Although this is the first study to evaluate the impact of MTM services in reducing polypharmacy, studies have demonstrated that MTM services are useful in identifying drug-related problems (Christensen, Roth, Trygstad, & Byrd, 2007). Pharmacists could make recommendations with the patient's provider to deprescribe an unnecessary drug or drugs with potential for a drug-drug interaction, thus leading to the reduction in the number of medications taken by an individual. The study by Christensen et al. assessed the attitudes of participants in an MTM program and showed an improvement in the knowledge and safe use of medications and the communication of patients with their providers. HIV patients who had personal encounters with community pharmacists may be able to express their concerns about their medication side effects freely. They may also discuss any issues about the medications thereby, providing an opportunity for the pharmacists to review and make changes to their medication.

The plausible explanation for the decrease in polyactive substance in this study could be that the recognition of the potential harms of polypharmacy through regular monitoring, and the review of patients' medications may create opportunities to deprescribe medications that are unnecessary or inappropriate. Community pharmacists conducting MTM assess the medications for the indication, dosage, drug-drug interactions, unnecessary drug duplication, and duration of therapy (Payne, 2016). This helps them to communicate with the primary physician to remove any unnecessary drug. Doucette et al. described the actions taken by community pharmacists and physicians during MTM services and his results corroborated the findings in this study. The study evaluated 150 elderly patients with chronic conditions who had MTM services with a community pharmacist. The pharmacists were able to identify 886 drug-related issues and made 659 recommendations to physicians to alter drug therapy, change or

stop a medication. The physicians accepted 47.4% of the recommendations made by the pharmacist for medication changes (Doucette, McDonough, Klepser, & McCarthy, 2005).

In this study, there were some significant predictors of the decrease in polyactive substances in medication over time with MTM intervention. Participants in all age group categories showed a significant reduction in polyactive substances. Likewise, in black non-Hispanics and Hispanics versus white non-Hispanic. Also, having Medicaid and multiple insurance providers when compared to private insurance. People who were retired or disabled were more likely to have an increase in the number of polyactive substances over time.

5.5 The Relationship between the change in CD4 counts and polyactive substances in medications used by PLWHA who had an MTM intervention.

Overall, there was an 11% improvement in CD4 counts among study participants pre-post program implementation. The average CD4 count increased by 61± 28 cells/mm^3. There was also an improvement in overall CD4 count categories as 87% final study population had a CD4+ cell count of ≥200 cells/mm^3 by the final study visit. An improvement of about 6% from baseline values. Although the population at follow-up was reduced, the increase in CD4 count over time suggests that the PCHCM program is effective. Our findings are similar to other studies that have shown that community pharmacist interventions are effective in improving CD4 counts (Barnes, Zhao, Giumenta, & Johnson, 2020; March et al., 2007). March et al reported an increase in baseline levels of CD4 count by 54 ± 78 cells/ mm^3. However, the two studies had a smaller sample size 47 and 34 HIV patients respectively and only compared the difference in means between the CD4 counts between the baseline and the endpoint (Barnes et al., 2020; March et al., 2007).

This study found a significant association between an improvement in CD4 count category and a decrease in polyactive substances over time with medication therapy management. The result in aim two and three confirms our postulation that medication therapy management leads to a reduction in polyactive substances and that a reduction in polypharmacy is associated with an improvement in viral outcomes CD4 count.

The possible explanation for the improvement in viral outcomes is that the reduction in the number of polyactive substances could have reduced the pill burden and resulted in improved adherence. A study reported an inverse relationship between increase in number of daily doses and adherence (Claxton, Cramer, & Pierce, 2001). Another study on people with multiple chronic diseases also reported that as the number of medications increases, the rate of compliance with medications decreases with resultant increase in the rate of hospital readmissions due to suboptimal disease control (Toh et al., 2014). These studies support our notion that a reduction in the number of pills could have played a role in improving adherence to medication intake, thereby improving treatment outcomes. Future studies would explore the relationship between the reduction in polypharmacy and adherence to medication.

Besides reducing the number of medications, studies have shown that pharmacist intervention has been effective in simplifying the dosage regimen, thereby improving adherence (Cocohoba, Murphy, Pietrandoni, & Guglielmo, 2012; Coleman et al., 2012). The fact that some patients have to take more than 20 pills every day or simultaneously indicate that the prescription may not be entirely appropriate. Also, compliance with these types of medication regimen is not expected to be perfect. Reducing the number of inappropriate medications is particularly important for people living with HIV who are faced with managing excessive amounts of medications. Studies have reported that when people have complex medication regimen, they tend to sometimes forget to take their drugs (Toh et al., 2014) leading to nonadherence.

Previous research using the data used for this study has demonstrated that MTM interventions are associated with increased adherence to medication regimen (Byrd, Hou, et al., 2019). Pharmacists have a fundamental role in promoting adherence to medication regimen among people with HIV. Hirsch et. al. found that patients using HIV MTM programs were more likely to be adherent to their medication refill pattern, which was used as a measure of adherence. They showed that those who had MTM services at HIV-specialized pharmacies had a medication possession ratio of 80% to 120% more than those using non-specialized community pharmacies (56.8% vs. 38.1 %, $P<0.0001$) (Hirsch et al., 2009). A study compared 4,254 HIV patients using HIV-focused community pharmacies with 11,679 patients using traditional pharmacies found that patients using HIV-focused pharmacies had higher prescription refill adherence. Multiple studies have correlated pharmacist-led adherence counseling and education during HIV intervention programs with improvement in medication adherence and improved HIV clinical outcomes (Byrd, Hardnett, et al., 2019; Henderson, Hindman, Johnson, Valuck, & Kiser, 2011; Hirsch et al., 2011; Ma, Chen, Chau, & Saberi, 2010). The relationship between increased CD4 count and decreased polyactive substances may also be attributed to the use of the appropriate medications during the intervention, thereby leading to improvement in CD4 count.

As this is the first piece of literature describing the association between HIV outcomes and polypharmacy during an MTM intervention, studies on the specific drug changes made by pharmacists during the MTM programs may further buttress the findings.

Also, the counseling and education offered during the MTM intervention may have played a role in improving medication use with the effect of improving HIV outcomes. Our study confirms this finding as we were able to show that the MTM intervention alone was significantly predictive of improvement in CD4 counts.

5.6 Relationship between the change in viral load and the change in the polyactive substances in medications used by people living with HIV/AIDS

Overall there was an improvement in viral suppression among the study participants by about 15%. Also, on average, the HIV RNA decreased by 6,699 copies/ml from pre-post-program implementation. A similar decrease in average viral load has been reported in studies that tried to evaluate the impact of interventions by community pharmacists on HIV outcome (Dilworth et al., 2018; March et al., 2007). The difference between this study and that of March et al. is that it is not a detailed MTM study. Although, it involved pharmacist review of medications, the study population was 34, with a majority being AIDS patients. The study compared the mean difference in viral load and CD4 counts but did not consider the effect of time in the study. The study did not find the association between HIV related outcomes and the change in polypharmacy.

This study also showed that over time with the MTM intervention, viral suppression increased with decrease in polyactive substances in medications used. Independently the number of polyactive substances alone without considering the pharmacist intervention was also associated with viral suppression. A potential explanation for this result is that pharmacist review of the patients' medical information allows them to evaluate the medications used for appropriateness and effectiveness. This intervention is pivotal to the recognition of barriers to effective treatment such as drug toxicity, drug-drug interactions, ARV resistance, and contraindicated therapy. The collaboration with physicians allows them to recommend a change in regimen to optimize treatment effectiveness.

Since pharmaceutical interventions enable the initiation, discontinuation, and consolidation of antiretrovirals and other drugs, there is a possibility that drugs are unnecessary drugs were discontinued. Further studies are required to elucidate this assumption.

Studies have demonstrated that medication therapy management with pharmacist intervention increases adherence to antiretroviral therapy ((Barnes, Zhao, Giumenta, & Johnson, 2020; Cocohoba, Murphy, Pietrandoni, & Guglielmo, 2012; Hirsch et al., 2011). The improved adherence reported with MTM services was associated with improvement in the viral suppression in HIV patients (Barnes et al., 2020) . The improvement in viral suppression in our study was consistent with a recent study by Barnes et al. They evaluated the impact of integrating a health-system pharmacy, which connects patient, provider, pharmacist, and pharmacy at the point of care on viral outcomes among 59 HIV patients. They reported that 95% increase in adherence among those that opted for integrated care compared to those who did not.

Also, in this study, being black, non-Hispanic was significantly predictive of improved CD4 count and viral suppression. This is worthy of note because black people account for 42 percent of all HIV infections, and studies have shown that they experienced persistent racial disparity and were more likely to have lower rates of viral suppression. A Center for Disease Control surveillance report shows that from 2011-2017, 40-56% of black persons had viral suppression compared to 53-68% of white persons (Johnson et al., 2019). The disparity in viral suppression rate has been explained by poor cultural competency among health care providers. A study has shown that patients with providers who have poor cultural competence are more likely to have a lower self-efficacy to manage their medications, thereby leading to low viral suppression (Saha et al., 2013). The pharmacists in the PCHCM program were provided with accredited training on cultural competency and preventing HIV stigma (Byrd, Hou, et al., 2019). The training received by the community pharmacists before starting the program may have helped to reach black participants, thereby improving HIV outcomes.

5.7 Limitations and Strengths

5.7.1 Strengths

The longitudinal analysis comparison on the same cohort considered the effect of time on reducing polyactive substance, viral suppression, and CD4 count, which establishes the durability of the effect. This is a major improvement on previous studies that did not consider the effect of time on improvement in these outcome measures. Also, the PCHCM program was conducted in 10 sites at 7 different states with a known high prevalence of HIV in the population, thereby increasing generalizability.

This is the first study to consider the polyactive substances in medications used by people living with HIV/AIDS. We were able to show that using the pill count may not be an accurate estimate of polypharmacy. With most HIV drugs being in fixed dose combinations, this study helped to show the true extent of polypharmacy in people living with HIV/AIDS.

5.7.2 Limitations of the study

Persons with no viral load and CD4 counts with dates in either the pre- or post-implementation period were excluded from the analysis in the third aim. It is possible that the persons with no viral load or CD4 count were not suppressed or were suppressed, thereby overestimating or underestimating the suppression and the immunologic response.

The CD4 count and viral load count had different lengths of measurement period lengths. However, there was no significant difference in calculations when comparing those with at least 365 days of data with those greater than 365 days.

The duration of use of the medications in the study, and the frequency of intake was not provided in the data and were not factored into the analysis. e.g., Drugs like Viagra are not used daily. Future studies should consider factoring the duration of use in the analysis.

The PCHCM was a demonstration project, and there were no control groups. Future studies should have a control group to be able to further compare the effect of MTM programs on polypharmacy.

5.8 Conclusion

This study demonstrated that there is a difference between the number of pills and the number of polyactive substances in medications used by persons with HIV. The use of polyactive substances in medications may be a better estimate of polypharmacy.

The patient-centered HIV care model integrated community-based HIV specialized pharmacists with primary medical providers to provide patient-centered care for PLWHA. This program, which seeks to identify and address HIV therapy-related problems, can lead to a reduction in polypharmacy. This dissertation showed that there was a reduction in polypharmacy over time (using the number of polyactive substances in medications as a measure). This study demonstrated that a reduction in polypharmacy improves viral suppression and CD4 count among patients who receive integrated MTM services. These findings are reflective of the efforts of the pharmacists and medical providers to optimize HIV treatment. HIV infected patients may especially benefit from the care provided by this type of patient-centered HIV care model.

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APPENDIX

Table 1 Recoding of variables for aim 1

Variables	Recoded Categories
Gender	**Gender**
Male	1= Male
Female	2= Female

Transgender	3= Transgender
Education	**Education**
Less than HS	1= Less than HS
HS only	2= HS only
Some college	3= Some college
College or above	4 = College or above
Unknown	5= Unknown/missing
Annual income	**Annual Income**
<$15,000	1= <$15,000
$15,000 - $30,000	2= >$15,000
>=$30,000	3= Unknown/missing
Unknown	
Housing Status	**Housing Status**
Currently homeless	1= Currently homeless
Not currently, but homeless in past year	2= Previously homeless
Homeless previously, but NOT homeless in past year	3= Never homeless
Never homeless	4= Unknown/missing
Unknown	
Employment status	**Employment status**
Unemployed	1= Unemployed
Employed	2= Employed or multiple jobs
Disabled	3= Disabled
Student	4= Student
Retired	5= Retired
Unknown	6= Unknown/missing
Multiple	
Insurance	**Insurance**
Private insurance	1= Medicaid

Medicaid	2= Medicare
Medicare	3= Multiple
Ryan White/ADAP	4 = Ryan White/ADAP
Uninsured	5 = Private insurance
Unknown	6 = Uninsured/Unknown/Missing
Multiple	
Race/ethnicity	**Race/ethnicity**
White, non-Hispanic	1= Black, non-Hispanic
Black, non-Hispanic	2= White, non-Hispanic
Hispanic	3= White, ethnicity unknown
Other	4= Hispanic
Unknown	5= Other/Unknown/Missing
Age	**Age**
Continuous variable	18 to 24
	25 to 34
	35 to 49
	50 or older
New Variables	**Pill count**
Sum of pills used by individuals	0= pill count >=5
	1= pill count <=4
Sum of polyactive substances in pills used by individuals	**Polyactive substances count**
	0= polyactive substance count >=5
	1= polyactive substance count <=4

Table 2 List of medications with polyactive substances of study participants in the initial data

Medication	Generic name	No of Polyactive substances
adderall	amphetamine/dextroamphetamine	2
adderal	amphetamine/dextroamphetamine	2
advair	fluticasone/salmeterol	2
albuterol/ipratr	albuterol/ipratopium	2
amlodipine atorvas	amlodipine/atorvastatin	2
amlodipine/ator	amlodipine/atorvastatin	2
anoro ellip	umeclidinum/villanterol	2
atenolol/chlort	atenolol/chlorthalidone	2
atropine/diphen	atropine/diphenhydramine	2
augmentin	amoxicillin/clavulanic	2
azor	amlodipine/olmesartan	2
Bactri	trimethoprim/sulfamethoxazole	2
bactrim	trimethoprim/sulfamethoxazole	2
breo ellipta	fluticasone/villanterol	2
budesonide/form	budesonide/formoterol	2
butalbital/acetam	butalbital/acetaminophen	2
caltrate	calcium/vitD3	2
cetirizine/pseu	cetirizine/pseudoephedrine	2
codeine/gua	codeine/guaifenesin	2
combigan op	brimonidine/timolol	2
combiv	ipratropium/albuterol	2
combivent re	ipratropium/albuterol	2
combivent respim	ipratropium/albuterol	2
complera	emtricitabine/rilpivirine/tenofovir	3
coricidin H	acetaminophen/chlorpheniramine	2
cortisporin	neomycin/polymyxin/hydrocortisone	3

descovy	emtricitabine/tenofovir	2
desenfriol	chlorpheniramine/phenylephrine/acetaminophen	3
dexacine	neomycin/polymyxin/dexamethasone	3
dulera	formoterol/mometasone	2
dyazide	hydrochlorothiazide/triamterene	2
epzicom	abacavir/lamivudine	2
EQL senna-s	docusate sodium/senna	2
evotaz	atazanavir/cobicistat	2
fioricet	acetaminophen/butalbital/caffeine	3
genvoya then	elvitegravir/cobicistat/emtricitabine/tenofovir	4
glucosamine chon	glucosamine/chondroitin	2
glyburide/metfo	glyburide/metformin	2
harvoni	ledipasvir/sofosbuvir	2
hydrocodone/ace	hydrocodone/acetaminophen	2
janumet	sitagliptin/metformin	2
jentadueto	linagliptin/metformin	2
kaletra	lopinavir/ritonavir	2
keppra amlo	levetiracetam/amlodipine	2
kombiglyze XR	saxagliptin/metformin	2
lisinopril/Hydrochl	Hydrochlorothiazide/lisinopril	2
lo loestrin	norethidrone acetate/ethinyl estradiol/Ferrous fumarate	3
lomotil	diphenoxylate/atropine	2
lortab	acetaminophen/hydrocodone	2
lotrel	amlodipine/benazepril	2
lotrisone	clotrimazole/bethamethasone	2
metoprolol/HCTZ	metoprolol/hydrochlorothiazide	2
neomycin/po	neomycin/polymyxin B	2
neosporin o	neomycin/bacitracin/polymyxin B	3

norco	acetaminophen/hydrocodone	2
novolin 70/30	insulin isophane/regular insulin	2
Novolog mix Fle	insul aspart protamine/insulin aspart	2
nystatin/tr	nystatin/triamcinolone	2
odefsey	emtricitabine/rilpivirine/tenofovir	3
ortho tri-cycle	estradiol/norgestimate	2
oxycodone/acetam	oxycodone/acetaminophen	2
pendex	guaifenesin/phenylephrine	2
percocet	oxycodone/acetaminophen	2
pericolace	docusate/senna	2
prezcobix	darunavir/cobicistat	2
senna s	docusate/senna	2
sprintec	estradiol/norgestimate	2
stribil	elvitegravir/cobicistat/emtricitabine/tenofovir	4
suboxone fi	buprenorphine/naloxone	2
symbic	budesonide/formoterol	2
symbicort	budesonide/formoterol	2
symbicort	budesonide/formoterol	2
triumeq	abacavir/dolutegravir/lamivudine	3
truvada	emtricitabine/tenofovir	2
vicodin	acetaminophen/hydrocodone	2
vicoprofen	hydrocodone/ibuprofen	2
viekira pak	ombitasvir/paritaprevir/ritonavir/dasabuvir	4

Table 3 Polyactive substances in the follow-up data

Brand name	Generic name	Polyactive substance count
Triumeq	Abacavir/dolutegravir/lamivudine	3
Epzicom	Abacavir/lamivudine	2
Fioricet	Acetaminophen/butalbital/caffeine	3
Coricidin H	Acetaminophen/chlorpheniramine	2
Tylenol with codeine	Acetaminophen/codeine	2
Lortab	Acetaminophen/hydrocodone	2
Norco	Acetaminophen/hydrocodone	2
Vicoden	Acetaminophen/hydrocodone	2
Albuterol/iprat	Albuterol/ipratoprium	2
Domeboro	Aluminium/calcium	2
Amlodipine/atorvastatin	Amlodipine/atorvastatin	2
Lotrel	Amlodipine/benazepril	2
Azor	Amlodipine/olmesartan	2
Augmentin	Amoxicillin/clavulanic	2
Adderall	Amphetamine/dextroamphetamine	2
Fiorinal	Aspirin/butalbital/caffeine	3

Evotaz	Atazanavir/cobicistat	2
Tenoretic	Atenolol/chlorthalidone	2
Atropine/diphenhydramine	Atropine/diphenhydramine	2
Combigan	Brimonidine/timolol	2
Symbicort	Budesonide/formoterol	2
Suboxone fi	Buprenorphine/naloxone	2
Butalbital/acetam	Butalbital/acetaminophen	2
Caltrate	Calcium/vitamin D3	2
Zyrtec-D	Cetirizine/pseudoephedrine	2
Desenfriol	Chlorpheniramine/phenylephrine/acetaminophen	3
Lotrisone	Clotrimazole/bethamethasone	2
Robitussin	Codeine/guaifenesin	2
Rezolsta	Darunavir/cobicistat	2
Prezcobix	Darunavir/cobicistat	2
Lomotil	Diphenoxylate/atropine	2
Senna-S	Docusate sodium/senna	2
Eql senna	Docusate/senna	2
Pericolace	Docusate/senna	2
Atripla	Efavirenz/emtricitabine/tenofovir	3
Biktarvy	Elvitegravir/cobicistat/emtricitabine	3
Genvoya	Elvitegravir/cobicistat/emtricitabine/tenofovir	4
Stribild	Elvitegravir/cobicistat/emtricitabine/tenofovir diproxyl fumarate	4
Complera	Emtricitabine/rilpivirine/tenofovir	3
Odefsey	Emtricitabine/rilpivirine/tenofovir	3
Descovy	Emtricitabine/tenofovir	2
truvada	Emtricitabine/tenofovir	2
ortho tri-cycle	Estradiol/norgestimate	2

Sprintec	Estradiol/norgestimate	2
	Estrogen/progesterone	2
Advair	Fluticasone/salmeterol	2
Breo Ellipta	Fluticasone/villanterol	2
Dulera	Formoterol/mometasone	2
Glucosamine chon	Glucosamine/chondroitin	2
Glyburide metformin	Glyburide/metformin	2
Pendex	Guaifenesin/phenylephrine	2
HCTZ/lisinop	Hydrochlorothiazide/lisinopril	2
Dyazide	Hydrochlorothiazide/triamterene	2
Vicoden	Hydrocodone/acetaminophen	2
Hydrocodone/acetam	Hydrocodone/acetaminophen	2
Vicoprofen	Hydrocodone/ibuprofen	2
Novolog mix 70/30	Insulin aspart protamine/insulin aspart	2
Humulin 70/30	Insulin isophane/insulin regular	2
Combivent	Ipratropium/albuterol	2
Combivir	Lamivudine/zidovudine	2
Harvoni	Ledipasvir/sofosbuvir	2
Keppra amlo	Levetiracetam/amlodipine	2
Jentadueto	Linagliptin/metformin	2
Kaletra	Lopinavir/ritonavir	2
metoprolol/HCTZ	Metoprolol/hydrochlorothiazide	2
Neosporin	Neomycin/bacitracin/polymyxin	3
neomycin/polymyxin B	Neomycin/polymyxin B	2
Dexacine	Neomycin/polymyxin/dexamethasone	3
Cortisporin	Neomycin/polymyxinB/hydrocortisone	3
lo loestrin	Norethidrone/estradiol/Ferrousfumarate	3
Nystatin/triamcinolone	Nystatin/triamcinolone	2

VieKira Pak	Ombitasvir/paritaprevir/ritonavir/dasabuvir	4
Percocet	Oxycodone/acetaminophen	2
Percocet	Oxycodone/acetaminophen	2
Kombiglyze XR	Saxagliptin/metformin	2
Janumet	Sitagliptin/metformin	2
bactrim	Trimethoprim/sulfamethoxazole	2
Bactrim DS	Trimethoprim/sulfamethoxazole	2
Septra DS	Trimethoprim/sulfamethoxazole	2
Bactrim albuterol	Trimethoprim/sulfamethoxazole/albuterol	3
Anoro ellipta	Umeclidinum/Villanterol	2

Sociodemographic characteristics of people living with HIV/AIDS in the study		
Demographics	**Total**	**P-value**
Gender (Total)	**765**	**<0.0001**
Male	555 (72.55)	
Female	193 (25.23)	
Transgender	17 (2.22)	
Education (Total)	**765**	**<0.0001**
Less than HS	98 (12.81)	
HS only	158 (20.65)	
Some college	101 (13.20)	
College or above	71 (9.28)	
Unknown/missing	337 (44.05)	
Annual Income (Total)	**765**	**<0.0001**
<$15,000	276 (36.08)	
>$15,000	126 (16.47)	
Unknown/missing	363 (47.45)	
Housing Status (Total)	**765**	**<0.0001**
Currently homeless	34 (4.44)	
Previously homeless	112 (14.64)	
Never homeless	290 (37.91)	
Unknown/missing	329 (43.01)	
Employment status (Total)	**765**	**<0.0001**
Unemployed	171 (22.35)	
Employed or multiple jobs	189 (24.71)	
Disabled	104 (13.59)	
Student	2 (0.26)	
Retired	13 (1.70)	
Unknown/missing	286 (37.39)	
Insurance (Total)	**765**	**<0.0001**
Medicaid	241 (31.50)	
Medicare	67 (8.76)	
Multiple	131 (17.12)	
Ryan White/ADAP	105 (13.73)	
Private insurance	96 (12.55)	
Uninsured/Unknown/Missing	125 (16.34)	
Race/ethnicity (Total)	**765**	**<0.0001**
Black, non-Hispanic	331 (43.27)	
White, non-Hispanic	185 (24.81)	
White, ethnicity unknown	65 (8.50)	
Hispanic	142 (18.56)	
Other/Unknown/Missing	42 (5.49)	
Age (Total)	**765**	**<0.0001**
18 to 24	27 (3.53)	
25 to 34	123 (16.08)	
35 to 49	251 (32.81)	

50 or older	364 (47.58)	

Table 4 Sociodemographic characteristics of study participants

Table 5 Classes of drugs used by the study participants

Classes of drugs used by the study participants	
	Frequency
Total	557
Antibiotics	40
Antihypertensive	37
Antiretroviral	35
Analgesics	30
Vitamin supplements	29
Hypoglycemic agent	26
corticosteroid	25
Anti-inflammatory agents	18
Antidepressants	17
Antifungals	17
Antihistamines	15
Antivirals	15
Antilipids	14
Anticonvulsants	12
Antipsychotics	12
Laxatives	10
Bronchodilators	9
Anxiolytics	8
Hormonal agents	8
Antiemetics	7
Dietary supplements	7
Anticholinergics	6
Anticoagulants	6
Calcium supplements	6
Stimulants	6
Antispasmodics	5
Antitussives	5
Contraceptives	5
Diuretics	5
Muscle relaxants	5
Phosphodiesterase-5-inhibitors	5
Proton pump inhibitors	5
Anti-tumor agents	4
Antidiarrheal	4
Anti-tuberculosis	4
Sedatives	4
Anaesthetic agents	3
Antiasthmatics	3
Iron supplements	3
Mineral supplements	3
Prostaglandin analogue	3

Thyroid hormone replacement	3
Anti-ulcer/GERD agents	3
Alpha antagonist	2
Anabolic steroid	2
Anti-angina drugs	2
Antiglaucoma	2
Antimuscarinic	2
Antiplatelet	2
Beta-blocker (Anti glaucoma)	2
Cholinergic agonist	2
Cholinesterase inhibitor	2
Dopamine agonist	2
Emollients	2
hypoglycemic agents	2
Muscarinic antagonist	2
Phosphate lowering agent	2
Probiotics	2
Smoking cessation agent	2
Supplement	2
Thyroid hormones	2
Xanthine oxidase inhibitor	2
Immunosuppressants	2
5 alpha reductase inhibitors	1
Alkalinizing agent	1
Anti-alcohol dependence	1
Anti-migraine	1
Anti-parkinsons	1
Anti-thyroid	1
Antiacid	1
Antiacne	1
Antiallergy	1
Antigout	1
Antihelminth	1
Antihypotensive	1
Antioxidant	1
Biphosphonate	1
Bisphosphonate	1
Cannabinoids	1
Cathecolamines	1
Colony stimulating factor	1
Contraceptives	1
Enzyme	1
Hematinic	1
Hormonal analog	2
Mood stabilizer	1

Opioid antagonist	1
Phosphate Binder	1
Potassium supplement	1
Protein	1
Salts	1
Selective noradrenaline reuptake inhibitor	1
Serotonin analogue	1
Steroid inhibitor	1

Table 6 Association between the difference in polyactive substances and pill count, and demographic variables

Association of polyactive substance/pill count difference with the demographic variables				
Variable	Parameter estimate	Standard Error	t Value	Pr > |t|
Intercept	2.07872	0.15704	13.24	<.0001
Male	Reference	Reference	Reference	Reference
Female	0.08742	0.11866	0.74	0.4615
Transgender	0.37332	0.33528	1.11	0.2659
Employed	Reference	Reference	Reference	Reference
Unemployed	-0.10211	0.13313	-0.77	0.4433
Disabled	-0.14465	0.15823	-0.91	0.3609
Student	-1.28824	0.94811	-1.36	0.1746
Retired	-0.23995	0.38138	-0.63	0.5294

Never homeless	Reference	Reference	Reference	Reference
Currently homeless	0.03467	0.24344	0.14	0.8868
previously homeless	-0.10812	0.14831	-0.73	0.4662
Uninsured	Reference	Reference	Reference	Reference
Medicaid	0.17442	0.16407	1.06	0.2881
Medicare	0.12863	0.21711	0.59	0.5537
multiple insurance	0.28581	0.17932	1.59	0.1114
Ryan white	0.36965	0.18917	1.95	0.0511
private insurance	0.39813	0.18803	2.12	0.0346
annual income > $15000	Reference	Reference	Reference	Reference
annual income < $15000	-0.09617	0.11989	-0.8	0.4227
50 years and above	Reference	Reference	Reference	Reference
18 - 24 years	-0.18469	0.27366	-0.67	0.5
25 - 34 years	-0.02579	0.14758	-0.17	0.8613
35 - 49years	0.11897	0.11173	1.06	0.2873
White Non-Hispanic	Reference	Reference	Reference	Reference
Black Non-Hispanic	-0.19337	0.12593	-1.54	0.1251
White Ethnicity unknown	-0.17617	0.19643	-0.9	0.3701
Hispanic	-0.05642	0.14442	-0.39	0.6962

Table 7 Analysis of the change in polyactive substances from the beginning to the end of the study

The change in polyactive substances over time adjusting for covariates						
Effect	Solution for fixed effect	Estimate	Standard	DF	t Value	Pr > |t|
Intercept		10.5313	0.6291	702	16.74	<.0001
Time		-2.7796	0.1658	724	-16.76	<.0001
Age	18-24	-3.7039	0.5831	724	-6.35	<.0001
Age	25-34	-2.5263	0.3258	724	-7.75	<.0001
Age	35-49	-1.1909	0.2476	724	-4.81	<.0001
Age	50 or older	0	.	.	.	.
Months		0.03964	0.02323	724	1.71	0.0883

Race/ethnicity	Black, non-Hispanic	-1.0019	0.2985	724	-3.36	0.0008
Race/ethnicity	Hispanic	-0.8847	0.34	724	-2.6	0.0095
Race/ethnicity	Other/unknown/missing	-0.6309	0.5772	724	-1.09	0.2748
Race/ethnicity	White, ethnicity unknown	0.6177	0.4549	724	1.36	0.1749
Race/ethnicity	White, non-Hispanic	0	.	.	.	.
Insurance	Medicaid	0.7664	0.3766	724	2.03	0.0422
Insurance	Medicare	0.5264	0.4893	724	1.08	0.2823
Insurance	Multiple	1.4402	0.4113	724	3.5	0.0005
Insurance	Ryan White/ADAP	-0.1356	0.4202	724	-0.32	0.747
Insurance	Uninsured/unknown/missing	0.6522	0.4572	724	1.43	0.1541
Insurance	Private insurance	0	.	.	.	.
Income	<15000	-0.07817	0.3413	724	-0.23	0.8189
Income	Unknown/missing	0.05914	0.3655	724	0.16	0.8715
Income	>15000	0	.	.	.	.
Education	HS only	0.1896	0.43	724	0.44	0.6595
Education	Less than HS	0.4713	0.4925	724	0.96	0.339
Education	Some college	0.178	0.4612	724	0.39	0.6996
Education	Unknown or missing	-0.3694	0.4065	724	-0.91	0.3639
Education	College or above	0	.	.	.	.
Housing status	Currently homeless	0.8444	0.5508	724	1.53	0.1257
Housing status	Previously homeless	0.5693	0.3395	724	1.68	0.094
Housing status	Unknown/missing	0.2922	0.2799	724	1.04	0.2968
Housing status	Never Homeless	0	.	.	.	.
Employment	Disabled	0.954	0.3796	724	2.51	0.0122
Employment	Retired	2.7582	0.8437	724	3.27	0.0011
Employment	Student	0.8339	2.0311	724	0.41	0.6815
Employment	Unemployed	0.2288	0.3313	724	0.69	0.49
Employment	Unknown/missing	0.4974	0.3471	724	1.43	0.1524
Employment	Employed or multiple jobs	0	.	.	.	.

Analysis of GEE Parameter Estimates							
Parameter	**Categories**	**Odds Ratio**	**Standard Error**	**95% Confidence Limits**		**Chi-sq**	**Pr >|Chisq**
Intercept		9.3960	3.8167	4.2383	20.8306	30.42	<.0001
Polyactive substance		0.9834	0.0184	0.9480	1.0201	0.80	0.3711
time		2.7725	0.9382	1.4283	5.3817	9.08	0.0026
Polyactive substance*time		0.9206	0.0321	0.898	0.9856	5.65	0.0175
Days between CD4 measurements		0.9994	0.0006	0.9981	1.0006	1.01	0.3155
CMR/TMR visits		1.0638	0.0738	0.9286	1.2188	0.80	0.3724
Age	18-24	1.0350	0.5492	0.3659	2.9283	0.00	0.9482
Age	25-34	0.8293	0.2485	0.4609	1.4921	0.39	0.5322
Age	35-49	0.6750	0.1533	0.4324	1.0535	2.99	0.0836
Age	50 or older	0	0	0	0	.	.
Race/ethnicity	Black, non-Hispanic	0.4107	0.124	0.2273	0.7423	8.68	0.0032
Race/ethnicity	Hispanic	0.864	0.3178	0.4201	1.7769	0.16	0.6911
Race/ethnicity	Other/unknown/missing	0.5515	0.3044	0.1869	1.6271	1.16	0.281
Race/ethnicity	White, ethnicity unknown	1.1613	0.5673	0.4457	3.0254	0.09	0.7596
Race/ethnicity	White, non-Hispanic	0	0	0	0	.	.
Insurance	Medicaid	0.5699	0.2209	0.2667	1.2181	2.1	0.1468
Insurance	Medicare	0.6691	0.3213	0.2611	1.7148	0.7	0.4027
Insurance	Multiple	0.9145	0.3979	0.3898	2.1456	0.04	0.8373
Insurance	Ryan White/ADAP	0.4924	0.2094	0.2139	1.1334	2.77	0.0958
Insurance	Uninsured/unknown/missing	0.4078	0.1841	0.1683	0.988	3.95	0.047
Insurance	Private insurance	0	0	0	0	.	.
Income	<15000	0.5528	0.1723	0.3001	1.0184	3.62	0.0572
Income	Unknown/missing	1.487	0.514	0.7552	2.9277	1.32	0.2511
Income	>15000	0	0	0	0	.	.
Education	HS only	1.1465	0.5243	0.4679	2.8094	0.09	0.765

Education	Less than HS	1.3261	0.6825	0.4836	3.6361	0.3	0.5835
Education	Some college	1.048	0.5192	0.3969	2.7674	0.01	0.9247
Education	Unknown or missing	0.8338	0.3542	0.3626	1.9171	0.18	0.6687
Education	College or above	0	0	0	0	.	.
Housing status	Currently homeless	0.9988	0.4464	0.4159	2.3983	0	0.9978
Housing status	Previously homeless	1.0921	0.3001	0.6373	1.8715	0.1	0.7485
Housing status	Unknown/missing	1.2435	0.3149	0.757	2.0426	0.74	0.3894
Housing status	Never homeless	0	0	0	0	.	.

Table 8 Relationship between CD4 count categories and change in polyactive substance over time

Table 9 The relationship between HIV RNA categories and change in polyactive substances over time

Analysis of GEE Parameter Estimates							
Parameter		**Odds Ratio**	**Standard Error**	**95% Confidence Limits**		**Chi-square**	**Pr >ChiSq**
Intercept		1.3728	0.541	0.6341	2.9719	0.65	0.4214
Polyactive substance total		1.0477	0.0224	1.0048	1.0926	4.77	0.029
Time		6.0977	2.5514	2.6853	13.8462	18.67	<.0001
Polyactive substance total*time		0.8926	0.0414	0.8151	0.9775	6.01	0.0142
Days between HIV RNA measurements		1.001	0.0006	0.9998	1.0021	2.76	0.0965
Number of CMR/TMR visits		0.937	0.0548	0.8356	1.0507	1.24	0.2654
Age	18-24	0.3519	0.1382	0.163	0.7596	7.08	0.0078
Age	25-34	0.322	0.0776	0.2008	0.5164	22.11	<.0001
Age	35-49	0.3915	0.0818	0.2599	0.5898	20.13	<.0001
Age	50 or older	0	0	0	0	.	.
Race/ethnicity	Black, non-Hispanic	0.5996	0.1391	0.3805	0.9449	4.86	0.0275
Race/ethnicity	Hispanic	1.5338	0.4164	0.9009	2.6114	2.48	0.1152
Race/ethnicity	Other/unknown/missing	0.7338	0.3405	0.2955	1.8222	0.44	0.5048
Race/ethnicity	White, ethnicity unknown	1.4522	0.6427	0.61	3.4571	0.71	0.3992

Race/ethnicity	White, non-Hispanic	0	0	0	0	.	.
Insurance	Medicaid	0.7715	0.2071	0.4559	1.3056	0.93	0.3339
Insurance	Medicare	0.9454	0.3654	0.4432	2.0167	0.02	0.8846
Insurance	Multiple	1.1189	0.3393	0.6175	2.0274	0.14	0.711
Insurance	Ryan White/ADAP	0.7819	0.2436	0.4246	1.4398	0.62	0.4296
Insurance	Uninsured/unknown/missing	0.6228	0.2077	0.3239	1.1974	2.02	0.1556
Insurance	Private insurance	0	0	0	0	.	.
Income	<15000	0.644	0.1615	0.394	1.0528	3.08	0.0793
Income	Unknown/missing	1.0015	0.2744	0.5853	1.7135	0	0.9957
Income	>15000	0	0	0	0	.	.
Education	HS only	0.9174	0.3068	0.4764	1.7668	0.07	0.7965
Education	Less than HS	0.7287	0.275	0.3478	1.5268	0.7	0.4016
Education	Some college	0.9975	0.3613	0.4905	2.0287	0	0.9945
Education	Unknown or missing	1.4903	0.4865	0.7859	2.826	1.49	0.2216
Education	College or above	0	0	0	0	.	.
Housing status	Currently homeless	0.7349	0.2672	0.3604	1.4986	0.72	0.3969
Housing status	Previously homeless	0.8516	0.2089	0.5265	1.3774	0.43	0.5126
Housing status	Unknown/missing	0.9433	0.2027	0.6191	1.4373	0.07	0.786
Housing status	Never Homeless	0	0	0	0	.	.

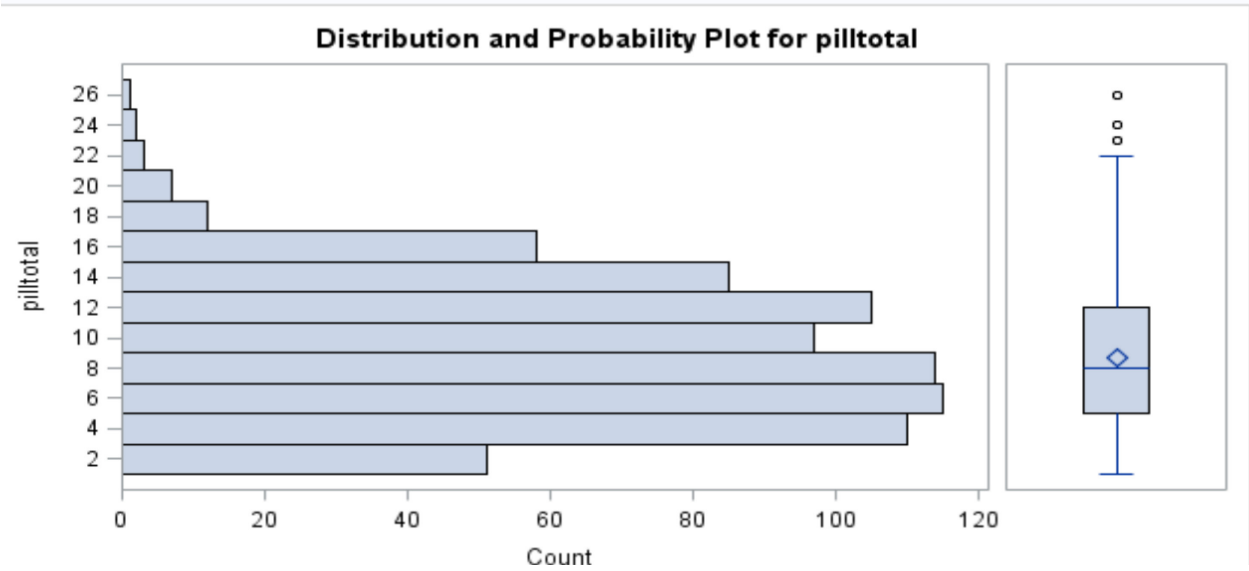

Figure 7 Distribution of the total number of pills used in the study

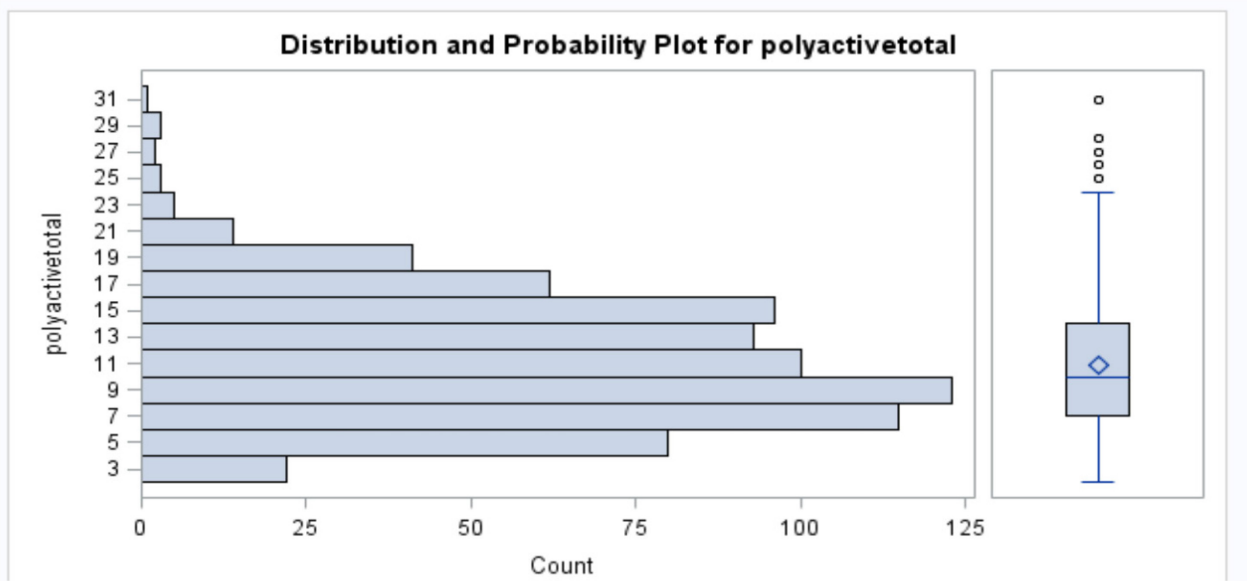

Figure 8 Distribution of the total number of polyactive substances in medications used by study participants

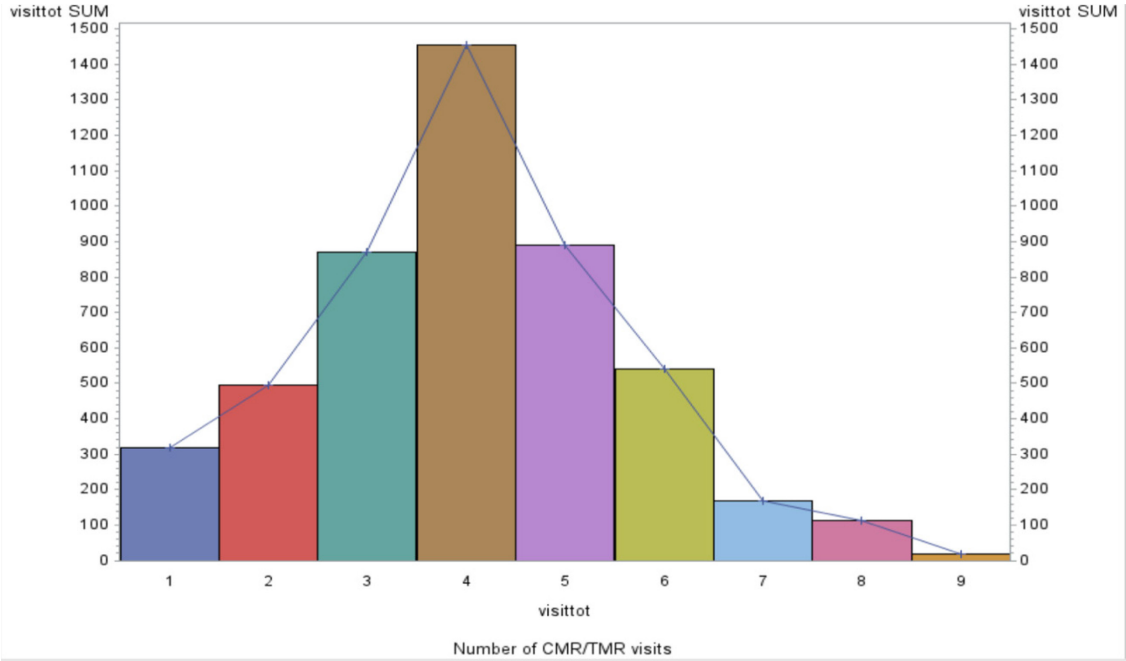

Figure 9 Number of Comprehensive and targeted medication reviews attended by study participants

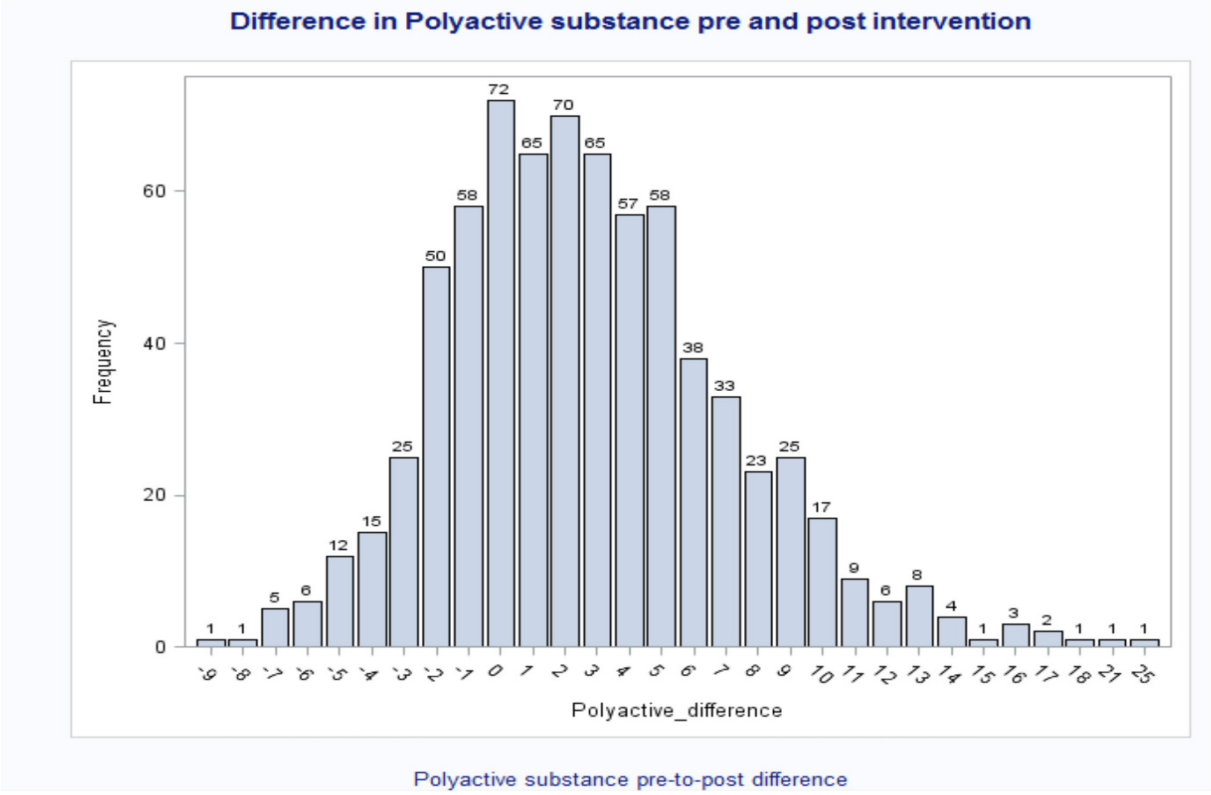

Figure 10 Difference in polyactive substance pre-to-post intervention

Appendix 2 Supplemental materials

Table 10 Changes made to medication entries in the initial data

Advair	Fluticasone/salmeterol
Amphetamine salt combo	Amphetamine/dextroamphetamine
Analpram	Topical hydrocortisone acetate
Androgel	Topical testosterone gel
Anoro ellipta	Umeclidinum and vilanterol
Anucort,	Hydrocortisone
Anusol	Hydrocortisone
Anusol HC	Hydrocortisone
Aptivus	Tipranavir
Aranesp	Darbepetin alfa
Aricept	Donezepil
Asacol HD	Mesalamine
ascensia microlet lancets deleted	
Ativan	Lorazepam
Atrovent and Atrovent HFA	Ipratropium bromide
Axiron	Topical testosterone gel
Azelastine HCL	Azelastine
B-12 Injection	Vitamin B12 injection
BD blunt fill needle deleted 02-108	
BD DIS needle deleted	
BDsyringedeleted	

BD luerlok syringe deleted	
Beclomethasone nasal and beclomethasone dipropionate HFA	Beclomethasone dipropionate , beclamethasone
Beconase AQ	Beclomethasone dipropionate
Benadryl	Diphenhydramine
Benazepril HCl	Benazepril
Benicar	Olmesartan
Bentyl	Dicyclomine
Benzonate	Benzonatate
Benztropine mesylate	Benztropine
Bethamethasone lotion	Bethamethasone
Biaxin	Clarithromycin
Bicillin	Penicillin G
Bicillin-L_A	Penicillin G
aeroeclipse 2 nebulizer Deleted	
aeroneb go nebulizer Deleted	
Bifidobacterium infantis	Probiotics
Boost liquid deleted	
Brainstrong prenatal	Multivitamins
Brilinta	Ticagrelor
Buproban	Bupropion
Bupropion HCL ER	Bupropion
Bupropion HCL ER	Bupropion
Bupropion SR	Bupropion
Bupropion SL	Bupropion
Buspirone HCl	Buspirone
Byetta	Exenatide

Calan and Calan SR	Verapamil
Calcium acetate	Calcium
Caltrate and vitamin D	Calcium and vitamin D
Calcium citrate and vitamin D	Calcium and vitamin D
Campral	Acamprosate
Canasa	Mesalamine
Carafate	Sucralfate
Cardizem ER	Diltiazem
Catapres tts	Clonidine – Transdermal clonidine
Ceftin	Cefuroxime
Celebrex	Celecoxib
Celexa	Citalopram
Cetirizine HCL	Cetirizine
Chantix	Varenicline
cheratussin ac	Codeine/Guaifenesin
Children's aspirin	Aspirin
Chlorpromazine HCL	Chlorpromazine
Choiceful multivitamin	Multivitamin
Cholecalciferol	Vitamin D3
Cialis	Tadalafil
Ciclopirox topical	Topical ciclopirox
Cipralex	Escitalopram
Citalopram hydrobromide	Citalopram
Citracal†+ D	Calcium + vitamin D
Claritin	Loratadine
Cleocin T	Topical clindamycin
Clindagel	Topical clindamycin
Clindamycin phosphate	Clindamycin

Clindamycin topical	Topical clindamycin
Clobetasol†0.05% Topical	Topical clobetasol
Clobetasol propionate	Topical Clobetasol
Clonidine HCL	Clonidine
Clonidine patch	Clonidine
Clopidogrel bisulfate	Clopidogrel
Clotrimazole topical	Topical clotrimazole
clotrimazole topical cream	Topical clotrimazole
Clotrimazole/bethamethasone	Topical clotrimazole/bethamethasone
Cobetasol	Topical Clobetasol
Cogentin	Benztropine
Colace	Docusate sodium
Colace/senna	Docusate sodium/senna
Colcrys	Colchicine
Combigan	Brimonidine/Timolol
Combivent	Ipratropium bromide /albuterol
Combivir	Lamivudine/zidovudine
Compazine	Prochlorperazine
Complera	emtricitabine, rilpivirine, and tenofovir disoproxil fumarate
Concerta	Methylphenidate
condom with nonoxynol-9 **deleted**	
Coreg	Carvedilol
Cozaar	Losartan
Creomulsion	Dextromethorphan
Crestor	Rosuvastatin calcium
Cyclobenzaprine HCL	Cyclobenzaprine
Cymbalta	Duloxetine

Cyproheptadine HCL	Cyproheptadine
Daily vitamin supplement	Vitamin supplement
Daliresp	Roflumilast
Depakote	Divalproex
Depression deleted	
Dexilant	Deslansoprazole
dialyvite	vitamin D
diclegis	Doxylamine/pyridoxine
diclofenac sodium	Diclofenac
diclofenac topical	Topical diclofenac
dicyclomine HCL	Dicyclomine
Diflucan	Fluconazole
Dilantin	Phenytoin
Dilaudid	Hydromorphone
Diltiazem CD, Diltiazem ER, Diltiazem HCL	Diltiazem
Diovan	Valsartan
Diphenhydramine HCL	Diphenhydramine
Diphenoxylate Hydrochloride/Atropine Sulfate	Diphenoxylate/atropine
Ditropan	Oxybutynin
Dilvaproex sodium	Dilvaproex
Docusate	Docusate sodium
Doxazosin mesylate	Doxazocin
Doxycycline hyclate	Doxycycline
Dulera	Mometasone furoate and formoterol fumarate dihydrate
Duloxetine Dr	Duloxetine
Duragesic patch	Fentanyl
Edurant	Rilpivirine

Effexor	Venlafaxine
Egrifta	Tesamorelin
Elavil	Amitriptyline
Emtriva	Emtricitabine
Enalapril maleate	Enalapril
Ensure clear liquid	Multivitamins ensure clear liquid
Epinephrine	Epinephrine autoinjection
Epipen	Epinephrine auto injection
Epivir	Lamivudine
Epogen	Epoeitin alfa
05-072 Epsom salt crystals deleted	
Epzicom	Abacavir/lamivudine
EQL senna S	Docusate sodium/senna
EQL vitamin D3 high potency	Vit D3
Ergocalciferol	Vitamin D2
Escitalopram oxalate	Escitalopram
Esomeprazole delayed release	Esomeprazole
Estrace	Estradiol
estrace vaginal cream	Estradiol
Estradiol valerate	Estradiol
Evotaz	Atazanavir/cobicistat
Famvir	Famciclovir
Farxiga	Dapagliflozin
Feosol	Ferrous sulphate
Ferrets	Ferrous fumarate
Flagyl	changed to metronidazole
Flexeril	Cyclobenzaprine
Flomax	Tamsulosin

Flonase, Flonase inh spray, Flonase nasal, Flonase nasal spray, Flonase susp	Fluticasone propionate
Flovent diskus, Flovent HFA	Fluticasone propionate
Flunisolide spray and flunisolide nasal spray	Flunisolide
Fluocinolone	fluocinonide topical
Fluocinonide cream	Fluocinonide topical
Fluphenazine	Fluphenazine
Fosamax	Alendronate
fps formula #5 deleted	
Fulyzaq	Crofelemer
Gabapentin ER	Gabapentin
Geodon	Ziprasidone
Glipizide ER	Glipizide
05-028 – Glucolet auto lancing device deleted	
glucotrol XL	Glipizide3
glucovance	Glyburide/metformin
Halcion	Triazolam
Haldol	Haloperidol
06-049 hepatitis B vaccine deleted	
Homolog KwikPen	Humalog
Humalog mix	Insulin lispro
Humulin 70/30	Insulin isophane and insulin regular
Huperzine A	Huperzine A (Herbal)
Hutone deleted	
Hydrocortisone cream	Hydrocortisone topical
Hydrocortisone oral	Hydrocortisone
Hydrocortisone suppository	Hydrocortisone
Hydrodiuril	Hydrochlorothiazide

Hydroxyzine hydrochloride	Hydroxyzinre
hyperparathyroidism deleted	
Hypodermic needle deleted	
Imdur	Isosorbide mononitrate
Imitrex	Sumatriptan
Imodium	Loperamide
Incruse ellipta	Umeclidinum
Indocin ER	Indomethacin
influenza Vaccine refuse – deleted	
Influenza vaccine deleted	
Insomnia deleted	
Ipatoprium	Ipratropium
Ipratopium albuterol, ipratropium albuterol solution,	Albuterol/ipratropium
ipratropium bromide nasal spr, ipratropium bromide nasal spray, ipratropium bromide nebulizer	Ipratropium
Intelence	Etravirine
Invokana	Canagliflozin
Isentress	Raltegravir
Janumet	Metformin/sitagliptin
Januvia	Sitagliptin
Jublia	Efinaconazole
Kaletra	lopinavir/ritonavir
KCL	Potassium chloride
Keflex	Cephalexin
Keppra	Levetiracetam
Ketoconazole 2%	Ketoconacole topical
Ketoconazole shampoo	Ketoconazole topical
Ketoconazole cream	Ketoconazole topical

Ketorolac oph	Ketorolac
Klonopin	Clonazepam
Klor con	Potassium chloride
Konbiglyze	Metformin/saxagliptin
Lamictal	Lamotrigine
Lamigan solution	Bimatoprost
Lamisil	Terbinafine
Lamisil cream	Terbinafine (topical)
Lamotrigine ER and XR	Lamotrigine
Lantus is	Insulin glargine
Lantus solostar	Insulin glargine
Lantus solostar pen	Insulin glargine
Lasix	Furosemide
Latuda	Lurasidone
Levaquin	Levofloxacin
Levimir	Insulin detemir
Levitra	Vardenafil
Levothyroxine sodium	Levothyroxine
Lexapro	Escitalopram
Lexiva	Fosamprenavir
Lialda	Mesalamine
Lidocaine patch	Lidocaine
Lilletta	Levonorgestrel acetate
Linzess	Linaclotide
Lipex	Simvastatin
Lipitor	Atorvastatin
Lisonopril	Lisinopril
lisinopril/HCTZ	Lisinopril/hydrochlorothiazide

Lithium carbonate	Lithium
Lithium carbonate ER	Lithium
Diphenoxylate/atropine	Atropine/diphenoxylate
Lomotil	Atropine/diphenoxylate
Lopid	Gemfibrozil
Lopressor	Metoprolol
Lortab	Acetaminophen/hydrocodone
Losartan potassium	Losartan
Hydrochlorothiazide losartan	Losartan hydrochlorothiazide
losartan/HCTZ	Losartan hydrochlorothiazide
Lotrel	Amlodipine/benazepril
Lotrisone	Topical cotrimazole/betamethasone
Low dose aspirin EC	Aspirin
Low dose ASA EC	Aspirin
Lumigan ophthalmic	Bimatoprost
Lunesta	Eszopiclone
Lyrica	Pregabalin
06-037 M-4 knee high stockings deleted	
Marinol	Dronabinol
Mebendazole powder	Mebendazole
Megace	Megestrol
Megestrol acetate	Megestrol
Medrol	Methylprednisolone
Mepron	Atovaquone
Metformin ER and Metformin HCL	Metformin
Methadone HCL	Methadone
Metoprolol succinate	Metoprolol
Metoprolol succinate ER	Metoprolol

Metoprolol tartrate	Metoprolol
Metorprolol XL	Metoprolol
Metrocream	Metronidazole
Miconazole nitrate	Miconazole
Minocin	Minocycline
Miralax	Polyethylene glycol
Miralax packet	Polyethylene glycol
Mobic	Meloxicam
Mometasone	Mometasone
Mometasone furoate/Formoterol fumara	Mometasone furoate/Formoterol fumarate
Monistat	Miconazole
Morphine ER, Morphine sulfate, Morphine Sulfate ER	Morphine
Motrin	Ibuprofen
Ms.contin	Morphine
Mutivitamin	Multivitamin
Mycogen	Nystatin/triamcinolone
Mycolog	Nystatin/triamcinolone
Naltrexone HCL	Naltrexone
Naprosyn	Naproxen
naproxen†	Naproxen
Nasacort AQ	Triamcinolone
Nasonex	Mometasone
Nephrocaps	Vitamin B complex /folic acid
Neurontin	Gabapentin
Nexium delayed release	Nexium
Nexium	Esomeprazole
10-061 Nexiva deleted	
Nexiva = catheter	

Nicoderm	Nicotine
Nicorette lezenge	Nicotine
Nicoderm CG	Nicotine
Nicotine patch	Nicotine
Nifedipin	Nifedipine
Nifedipine ER	Nifedipine
Nifedipine XL	Nifedipine
Nifedipine ER and Nifedipine Xl	Nifedipine
Nittrofurantoin macrocrystals	Nitrofurantoin
Nitrostat	Nitroglycerin
Nizoraland Nizoral shampoo	Ketoconazole
Normodyne	Labetalol
Norvasc	Amlodipine
Norvir	Ritonavir
Novolog 70/30	Insulin aspart/insulin aspart protamine
Novolog mix	Insulin aspart/insulin aspart protamine
Novolog mix flex pen	Insulin aspart/insulin aspart protamine
Nystatin oral suspension	Nystatin
Ocuflox solution	Ofloxacin
Odansetron	Ondasetron – 04-065
Ofloxacin ophthalmic	Ofloxacin
Ofloxacin ophthalmic solution	Ofloxacin
Oscal D3	Calcium/vitamin D3
03-042 osteopenia deleted	
Oxandrin	Oxadrolone
Oxycodone and acetaminophen	Oxycodone/acetaminophen
Oxycotin	Oxycodone
Oysco	Calcium/Vit D

One a day womens tab?????	Consider changing to multivitamin
Onglyza	Saxagliptin
Optimal D3	Vitamin D3
Ortho Tri-Cyclen	Norgestimate-Ethinyl Estradiol
Pamelor	Nortriptyline
Pancreaze	Pancrelipase
Pataday	Olopatadine
Paxil	Paroxetine
Ppenicillin	Penicillin
Penlac Nail lacquer	Ciclopirox
Pepcid	Famotidine
Peridex	Chlorhexidine gluconate ??? mouth wash
Persantine	Dipyridamole
Phenergan	Promethazine
Phenytoin sodium and Phenytoin sodium ER	Phenytoin
Phos Lo	Calcium acetate
09-070 Physical exercise deleted	
Plavix	Clopidogrel
Pletal	Cilostazol
pneumovax 23	Pneumococcal vaccine
Pradaxa	Dabigatran
Pravachol	Pravastatin
Pravacol	Pravastatin
Pravastatin sodium	Pravastatin
Pred forte suspension	Prednisolone acetate then to prednisolone
Prednisone ophthalmic	Prednisone
Prenatal multivitamin	Multivitamins
Prevacid	Lansoprazole

Prevnar, Prevnar 13 and Prevnar vaccine	Pneumococcal vaccine
Prezcobix	Darunavir/cobicistat
Prezista	Darunavir
Prilosec	Omeprazole
Pristic	Desvenlafaxine
ProAIr	Albuterol
Proair HFA	Albuterol
Prochlorperazine maleate	Prochlorperazine
Prochlorperzine	Prochlorperazine
Prograf	Tacrolimus
Promethazine with codeine	Promethazine/codeine
Propanolol ER	Propranolol
Proscar	Finasteride
Protonix	Pantoprazole
Protonix 40 mg	Pantoprazole
Proventil and Proventil HFA	Albuterol
Proventil inhaler	Albuterol
Provigil	Modafinil
Prozac	Fluoxetine
Pyridium	Phenazopyridine
Qnasl	Beclomethasone dipropionate
Quetiapine fumarate	Quetiapine
†Quetiapine	Quetiapine
Qvar	Beclomethasone dipropionate
Rectiv	Nitroglycerin
Reglan	Metoclopramide
Relpax	Eletriptan
Remeron	Mirtazapine

Requip	Ropinirole
Restasis	Cyclosporine (Ophthalmic solution)
Reyataz	Atazanavir
05-079 – rhinitis deleted	
Riomet	Metformin
Risperdal	Risperidone
Robitussin	Guaifenesin
Robaxin	Methocarbamol
Roxanol	Morphine
Roxicet	Oxycodone/acetaminophen
06-004 Selsun blue shampoo deleted	
Selzentry	Maraviroc
Senokot	Sennosides
Senna	Sennosides
Senna s	Docusate sodium/sennosides
Senna plus	Docusate sodium/sennosides
Sennalax	Sennosides
Septra DS	Sulfamethoxazole/trimethoprim
Serevent	Salmeterol
Seroquel	Quetiapine
Serostim	Somatropin
Shower chair deleted	
Silvadene	Silver sulfadiazine
Singulair	Montelukast
Sitagliptan	Stagliptin
Slidenafil	Sildenafil
Solvadi	Sofosbuvir
Soma	Carisoprodol

Spiriva	Totropium bromide
Sprintec	Norgestimate/ethinyl estradiol
Stendra	Avanafil
Strattera	Atomoxetine
Strovite	Vitamin B complex/Vitamin c
Sustiva	Efavirenz
Tamiflu	Oseltamivir
Tamsulosin ER	Tamsulosin HCL
Tapazole	Methimazole
Tarivid	Ofloxacin
Tenoretic	Atenolol/ chlorthalidone
Tercanozole	Terconazole
tessalon perles	Benzonatate
Tesarotene	Tazarotene
Tivicay	Dolutegravir
Tizanidine HCL	Tizanidine
Tobacco patch	Nicotine patch 02-012
Tobramycin 0.3% Ophthalmic Solution	Tobramycin
Topamax	Topiramate
Topical Nifedipine 0.5 %	Nifedipine Topical
Toprol XL	Metoprolol
Total B/C tablet	Vitamin
Toviaz	Fesoterodine
Tradjenta	Linagliptin
Tradozone	Trazodone
Tramadol ER	Tramadol
tramadol†	Tramadol
Trazadone	Trazodone

Travatan	Travoprost
Trazodone HCL	Trazodone
Triacet	Triamcinolone
Triamcinolone acetonide	Triamcinolone
Triamcinolone cream, triamcinolone ointment	Triamcinolone topical
Triamcinolone	
Tricor	Fenofibrate
Triglide	Fenofibrate
Trileptal	Oxcarbazepine
04-034 – Tuberculosis deleted	
Tylenol	Acetaminophen
Tylenol arthritis	Acetaminophen
Tylenol w/codeine	Acetaminophen/codeine
Uloric	Febuxostat
Ultram	Tramadol
Urea lotion	Urea Topical
valacyclovir†	Valacyclovir
Valcyte	Valganciclovir
Valium	Diazepam
Valtrex	Valacyclovir
Vascepa	Lcosapent Ethyl
Vasotec	Enalapril
Vastatin calcium	Atorvastatin calcium
VC forte	Multivitamins
Venlafaxine XR	Venlafaxine
Ventolin	Albuterol
Ventolin Inhale	Albuterol
Vesicare	Solifenacin

Vicoprofen	Hydrocodone and Ibuprofen
Victoza	Liraglutide
Viracept	Nelfinavir
Viramune	Nevirapine
Viread	Tenofovir
Vitamin D 50,000IU	Vitamin D
Vitamin D supplements	Vitamin D
Vitamine E cream	Vitamin E topical
Voltab	Multivitamins
Voltaren	Diclofenac
Vyvanse	Lisdexamfetamine
Warfarin sodium	Warfarin
Wellbutrin	Bupropion
Xalatan	Latanoprost
Xanax	Alprazolam
Xarelto	Rivaroxaban
Xopenex	Levalbuterol
Xyzal	Levocetirizine
Zantac	Ranitidine
Zemplar	Paricalcitol
Zerit	Stavudine
Zestoretic	Lisinopril/hydrochlorothiazide
Zetia	Ezetimibe
Ziagen	Abacavir
Zofran	Ondansetron
Zofran ODT	Ondansetron
Zoloft	Sertraline
Zovirax	Acyclovir

Zpak	Azithromycin
Zolpidem tartrate and Zolpidem CR	Zolpidem
Zyrtec	Cetirizine

Notes

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Disclaimer

The findings and conclusions of this dissertation are those of the author and do not represent the official position of the Centers for Disease Control and Prevention.

Patient-centered HIV Care Model Team: Michael Aguirre, Osayi Akinbosoye, David M. Bamberger, Ben Bluml, Katura Bullock, Diane C. Burrell, Tim Bush, Clifton Bush, Kathy K. Byrd, Chad Cadwell, Nasima M. Camp, Roberto Cardarelli, Terri Clark, Patrick G. Clay, Andrew Crim, Angela Cure, Kristin Darin, Traci Dean, Ambrose Delpino, Michael DeMayo, Shara Elrod, Ashley L. Eschmann, David

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