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Regimen Complexity in Aging HIV-Infected Veterans: Data from HAVACS

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University of Vermont

2011

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An abstract of

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Abstract

Regimen Complexity in Aging HIV-Infected Veterans: Data from HAVACS

By Daniel J Reichman

Advances in antiretroviral (ARV) medication regimens have greatly contributed to the increased survival and subsequent aging of the population of persons living with HIV/AIDS (PLWHA). While the total daily pill burden for ARV and non-ARV medications has been examined by age in HIV-infected patients, regimen complexity is another aspect of polypharmacy that has been associated with adherence and clinical outcomes. The HIV Atlanta VA Cohort Study (HAVACS) includes all HIV-infected veterans seen at the Atlanta VA Medical Center since 1982. The Medication Regimen Complexity Index (MRCI), developed by the University of Colorado Denver, was used to determine the complexity of a patient's medication process for a randomly selected subset of 146 patients prescribed medication and seen between January 1, 2004 - October 31, 2014. The MRCI score takes into account the route, dose, and frequency. The higher the MRCI scores, the greater the regimen complexity. Chi-square, Fischer's exact tests, and one-way analysis of variance were used to compare the MRCI score across age groups. Patients were separated by age into three categories; Age Group 1: 23-44 years (mean 37) (n=47), Age Group 2: 45-55 years (mean 47) (n=50), and Age Group 3: 56-92 years (mean 63.6) (n=49). There was a statistically significant difference in MRCI mean score among the groups ($p<0.0001$). Mean MRCI scores by Age Group are: Group 1 mean score of 10.3, Group 2 mean score of 14.0 and Group 3 mean score of 20.9. Figure 1 shows the distribution of MRCI scores among the three age categories. Further analysis showed that there was a statistically significant difference in MRCI score means between Age Groups 1 and 3 ($p < 0.0001$) and Age Groups 2 and 3 ($p= 0.004$). The magnitude of the MRCI score varied significantly across the three age groups. Greater regimen complexity was seen with the oldest age group. Individually, age and regimen complexity have been associated with nonadherence. As PLWHA continue to age, measures of polypharmacy will be an essential component of clinical success.

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Chapter I. Literature Review

HIV Mortality: Then and Now

The human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) were initially recognized in 1982 and was quickly identified as the leading cause of death among young Americans in the 1980's and 1990's. Over 640,000 people were diagnosed with HIV through 1997 and, reportedly, at least 385,000 individuals had died due to this viral illness during this time (1). The onset of this epidemic greatly challenged physicians who were left to care for patients afflicted with a disease they knew very little about. Physicians were expected to manage patient care with newly FDA approved medications they were not familiar with in varying regimens that had not been clearly supported through scientific research. By 1998, there were over a dozen antiretroviral (ARV) medications including reverse transcriptase enzyme inhibitors and protease inhibitors. Studies reported over 1,000 ways that these medications could be taken in combination; some of which had conflicting results (1). Research was desperately needed to help establish effective regimens that were capable of improving the health of HIV infected individuals and reduce the burden of disease.

By the early 2000's, improved evidence based combination antiretroviral therapies (cART) and highly active antiretroviral therapies (HAART) were capable of controlling viral load as well as maintaining high CD4 levels (2-3). There appeared to be little difference in patient outcomes, including CD4 levels, viral load and progression to AIDS or death, when comparing the different HIV treatment regimens used today (2). Mocroft

et al., observed that the median CD4 levels among HIV infected individuals increased from 164 cells/uL in 1994, before HAART were used, to 424 cells/uL in 2001, after HAART were implemented (3). Patients with a CD4 count of 50 cells/uL or less decreased from 28.0% in 1994 to 2.6% in 2001. Patients with a CD4 count of greater than 200 cells/uL increased from 42.2% in 1994 to 84.5% in 2001. The incidence of AIDS was also found to be about 50% lower between 1998 and 2002 (late-HAART use) as compared to 1994-1995 (pre-HAART use).

Without the initiation of treatment, the median survival time after seroconversion, or when anti-HIV antibodies are first detected in the blood, is eight to ten years (4). The introduction of ARV therapies has greatly increased the life expectancy of those infected with HIV. The combined AIDS/mortality rate related to HIV decreased from 43.5 per 100 person-years of follow up in 1994 to less than five per 100 person-years of follow up in 2001 after the introduction of HAART (3). Similar results were found in a study reporting the excess mortality rates among HIV positive patients from 1996 to 2006. These rates decreased from 31.4 per 1000 person-years to 6.1 per 1000 person-years; a 94% decrease in excess mortality rates. Nakagawa et al. used the rates of effectiveness of antiretroviral therapies in 2010 and computer simulation to model HIV infection and life expectancy of men who have sex with men (MSM) aged 30 years old. It was found that this population's median life expectancy ranged between 71.5 to 75 years depending on their CD4 count when diagnosed with HIV. The median life expectancy of the same demographic who were not infected with HIV was estimated to be 82.0 years. On average, this accounts for a 7-year reduction in life expectancy due to HIV infection (5).

A similar computer simulation was performed by Losina et al. comparing multiple cohorts of individuals in the general population of the United States with similar demographics; one group infected with HIV and the other not infected (6). It was determined that the life expectancy of HIV infected individuals at 33 years old, was an additional 34.6 years and the life expectancy of uninfected individuals, starting at 33 years of age, was an additional 42.9 years. This is roughly 8 years of life lost due to HIV infection. The increase in longevity that has been observed in those infected with HIV, which can mainly be attributed to the implementation of anti-retroviral therapies, has introduced a new challenge: how to care for the aging HIV infected population.

Characteristics of the Aging HIV Population

Today, it is estimated that there are 38.8 million people living with HIV (PLWH) and 10% of these individuals are over 50 years old (7). There are about 1.4 million PLWH in the United States. From 2007 to 2015, the percentage of PLWH in the US aged 50 years or older increased from 28% to about 50% (8). It is estimated that by the year 2030 this percentage will reach 70% Not only are patients with HIV living longer, but older individuals remain at risk of contracting HIV adding to the growing number of infections in these age groups. In 2011, it was estimated that there were 6,263 new cases of HIV in the US among individuals aged 50-59 years old (9). There were also 2,177 new cases of HIV among persons aged 60 years or older. Individuals 50 years or older made up over 17% of new cases of HIV in 2011. Reports from 2005-2008 showed patients younger

than 50 were diagnosed with HIV annually at a rate three times greater than that of older individuals. Despite lower rates of diagnosis, older patients engage in a number of behaviors that continue to put them at risk for HIV contraction.

Older persons are often unaware that they are at risk of contracting HIV. Studies show that older individuals (50 years or older) are uninformed about the mechanism for the transmission of HIV, often do not get tested for HIV infection (one study showed this was over 90%), and believe HIV mainly affects younger individuals and sexual minority groups (9-10). In a study conducted in 1995 on the knowledge of AIDS among older individuals, women 45 years and older answered 55% of the questions correctly on the AIDS Risk Behavior Knowledge Scale. Results also showed that 81% of these older women who had a primary sexual partner had unprotected sex. Rates of unprotected sex among older individuals has not changed in recent years.

In 2015, a review on sexual risk behaviors among older individuals within the last 10 years showed that men and women aged 50 years or older who reported having unprotected sex in their last sexual encounter was 80% and 76%, respectively (9). The prevalence of condom use was shown to decline with age. 24.3% of individuals aged 50-59 years old and 17.1% of individuals aged 60-69 years old reported using a condom during their last sexual experience. A study conducted in the US in 1996 showed that heterosexual older women with an HIV infection were less likely to have used a condom or have been tested for HIV before they were diagnosed (10).

It is generally believed that the older population is sexually inactive and are often not asked about their sexual health by their physician. A study conducted in 2011 reviewed 360 medical charts from two outpatient facilities at the University of Colorado School of Medicine (11). It was found that documenting sexual history was less likely to occur as the patient's age increased. A survey reporting the national prevalence of sexual activity, behaviors, and problems conducted in 2007 among men and women aged 57-85 years showed that the prevalence of sexual activity was 73% among individuals aged 57 to 64 years old. Prevalence declined to 53% among individuals 65 to 74 years old and was 26% among persons 75-85 years old. Roughly half of the sexually active participants reported having at least one sexual problem, and in total only 38% of men and 22% of women had discussed sex with a physician since turning 50 years old (12). It is important for medical providers to take full patient histories even when it comes to documenting topics they are uncomfortable addressing. This is necessary in order to properly educate older patients regarding risk factors for HIV transmission and to help prevent future infections.

Rates of HIV infection are disproportionate when comparing sexes and different racial/ethnic groups among the general US population. There is a higher prevalence of HIV cases in males as compared to females. In 2010, 80% of newly diagnosed cases were male (9). As of 2014, estimated rates of HIV infection diagnoses among individuals aged 50-54 were highest for the Black/African American population (45.6 per 100,000). Rates (per 100,000) of HIV diagnosis were 19.4 for Hispanics/Latinos and 8.4 for White

individuals. Similar disparities regarding rates of diagnosed HIV infections were also observed among those aged 55-59 (13).

MSM are at an increased risk of HIV infection and represent the largest proportion of HIV infection among males. In 2009, 61% of new infections were MSM (14). A similar trend is observed in older Americans. In 2010, among males aged 50 years and older, 60% of HIV diagnoses were MSM, 23% were through heterosexual contact, and 14% were intravenous drug users (IDU) (9). Among females aged 50 years and older, 82% of HIV diagnoses were through heterosexual contact and 18% were attributed to IDU. IDUs are in a high-risk category of becoming infected with HIV, but alcohol and non-injection drug users are also at risk of HIV infection.

Current research shows that 5% of adults aged 50 years and older have used illegal drugs in the past year; this estimate is expected to double by 2020 (15). Individuals who abuse drugs and alcohol are more likely to partake in sexually risky behaviors as compared to those who do not use drugs/alcohol (9). Multiple studies have reported an increased risk of irregular/inconsistent condom use among older adults who use drugs and alcohol. Especially for older MSM, alcohol and drug use has been associated with unprotected anal intercourse. Higher rates of nitrate inhaler (poppers) have been seen among older bisexual/gay communities that and this has been correlated with increased sexual-risk behaviors as compared to other substances.

The older population also has physiologic factors that may contribute to their increased risk of HIV infection and seroconversion. One of these factors includes deterioration of the body's cells and tissues resulting in decreased organ function and inability for the body to restore homeostasis when infection is introduced (16). These individuals may have more difficulty fighting infection due to waning immunity associated with older age. Other risk factors among older individuals includes the decreased ability to effectively metabolize medications and vaginal and anal wall thinning which increases the chance of atrophy and tearing during intercourse. Older individuals are more likely to seroconvert once exposed to HIV as well as progress to AIDS.

There is evidence showing older patients have a slower immunological response to HAART which may lead to a poorer prognosis (17). One study showed patients older than 50 years old had a significantly slower CD4 cell increase after beginning HAART as compared to patients under 50. The risk of HIV disease progression was found to be 1.5 times greater among individuals older than 50 who were on HAART as compared to younger patients. Older patients on HAART were also more likely to die or have an AIDS-defining event. Those with HIV are more likely to have comorbidities affecting their health and HIV disease progression.

Comorbidities in the Aging HIV Population

Health management of a patient with HIV becomes very complicated when there is also a need to simultaneously treat comorbid conditions. Schouten, J., et al compared rates of cardiovascular and renal disease among an elderly cohort with HIV infection and a control group without infection (18). These conditions included hypertension, myocardial infarction (MI), peripheral arterial disease, and impaired renal function. It was found that the HIV infected group, older than 50 years old, had a significantly higher rate of age-associated noncommunicable comorbidities (AANC). It was also found that the odds of having AANC among those with HIV infection were about 1.6 times higher than their uninfected counterparts. Other studies have found similar results when researching comorbid illnesses in populations with HIV infection.

It has been reported that those infected with HIV are nearly two times more likely to have a Myocardial infarction (MI) as compared to the uninfected population (8). This increased risk for an MI can be attributed to both increased age and prolonged therapy with HAART (17). There is also an increased risk for both liver and renal disease among HIV positive patient with chronic exposure to ARV medications. Other studies have shown that HIV positive patients who are on cART have a prevalence of diabetes mellitus that is almost 5 times higher than those who are HIV seronegative. In addition, there is also an increased risk for metabolic syndrome while using cART; between 17% and 24% of HIV infected patients have a form of metabolic syndrome. One study determined patients with HIV had a four times greater incidence of diabetes as compared

to those without HIV (19). There is also a two-fold greater risk of cancer among those who are HIV positive as compared to the uninfected population. It can be difficult to treat PLWH due to possible drug-drug interactions when they are taking medications for other illnesses. Prognosis can also be affected because of a missed or late diagnosis of HIV.

Multiple studies have shown that HIV is diagnosed during later stages in older patient as compared to younger ones (17). Many of the symptoms associated with HIV such as fatigue, weight loss, memory loss, neuropathies, or skin abnormalities may be mistaken as part of several diseases common in the elderly population (16). Pneumocystis carninii pneumonia (PCP) is a very common opportunistic infection in older adults. It is often diagnosed as congestive heart failure (CHF) or pulmonary disease. Dementia, not uncommon in the elderly population, has been shown to be present in 25% of HIV positive patients 50 years or older. Neurocognitive impairment, which is a major health consideration in the aging population, may be worsened by HIV infection (20). Patients diagnosed later in their HIV development have higher rates of progression to AIDS and death (21). One study showed patients who were diagnosed with HIV at 60 years or older had a 70% greater probability of dying as compared to patients diagnosed before 60 years old (16).

Both hepatic and renal function naturally decrease with age and this may impair drug elimination including ARV medications (20). This needs to be a consideration for

clinicians taking care of the older HIV patient population as the literature includes most often includes clinical trials include patients with normal organ function and very few participants are over 50 years old. Patient conditions need to be closely monitored to assess for medication dosage adjustments. Guidelines currently emphasize the importance of paying attention to older patients renal, liver, cardiovascular, metabolic, and bone health as ARV medications may have deleterious effects on these body systems. Bone density scans are also recommended for male patients older than 50 and postmenopausal women to determine if changes in medications are warranted due to fragility.

The implications of starting ARV therapy during later stages of the disease continues to be studied, although it is believed that starting ARV medications at later stages results in less CD4 cell recovery and immunologic response (20). Clinicians need to be mindful of the risk factors affecting the diagnosis and prognosis of older patients infected with HIV and use this knowledge to better serve this population.

Polypharmacy, Pill burden and Adherence

Increased rates of comorbidities in the HIV aging population has contributed to increased polypharmacy and pill burden. Polypharmacy is defined as taking five or more prescribed medications (19). Gimeno-Gracia, M., et al conducted a study over a one-year period showing that among a cohort of HIV positive patients aged 50 years or older, 58% were taking five or more separate medications in addition to their antiretroviral medications

(22). Data suggests polypharmacy is related to poorer health outcomes in the older population, drug-drug interactions, and nonadherence to medication regimens.

Polypharmacy is associated with increased frailty, which includes weight loss, weakness, and low activity (23). It has also been associated with disability defined as needing help with one more activities of daily living (ADL), increased mortality, and higher number of falls. Patients taking ARVs including protease inhibitors and Maraviroc, a CCR5 receptor antagonist, in combination with cardiovascular medications were found to be at increased risk of drug-drug interactions (19). Another study found that patients older than 42 years old with four or more comorbidities who were taking three or more ARVs or a protease inhibitor were at an increased risk for drug-drug interactions (24). Medications such as antihypertensives, statins, antiarrhythmics, anticoagulants, H2 blockers, antidepressants, antibiotics, steroids, narcotics and many others interact with ARVs. Drug interactions with ARVs most commonly occur with cardiovascular agents, central nervous system medications, and methadone. The older HIV positive population needs careful medication regimen reconciliation, as they are at a higher risk due to polypharmacy and subsequent adverse health events.

The literature shows that polypharmacy is also associated with increased risk for nonadherence among any patient population (25). Studies focused only on the HIV positive population also show that polypharmacy or higher daily HIV pill count puts patients at risk for nonadherence. One study found that only 54% of their study cohort

were completely adherent to their cART regimen (26). Ensuring patients can maintain adherence to their ARVs is critical for viral suppression and reduces the risk for viral resistance, opportunistic infections, and hospitalization. Studies have shown that taking simpler or single tablet ARV medication regimens results in better adherence, lower risk of hospitalization and longer time to hospitalization as compared to patient taking a multiple tablet regimen (20, 27). Adherence has also been shown to improve with once daily ARV regimens rather than twice-daily regimens. ARV medication regimens today are much simpler to take and better tolerated than they used to be. The pill burden in these regimens has decreased drastically over the past 10 years. One study showed patients on average were taking 6.2 ARV pills daily in 2005, which decreased to 4.1 by 2012 (28). The medication regimens over this period were also found to move towards a once daily dosing; increasing from 4.1% in 2005 to 49.1% in 2012. Current guidelines for the use of ARTs in HIV infected individuals focus on reducing pill burden and implementing once daily medication regimens with fewer side effects to help increase levels of adherence.

In addition to pill burden and complexity of prescription regimen, there are many other factors that contribute to patient adherence to their ART. Other issues to consider include mental illness or depression, neurocognitive impairment, limited social support, substance abuse, homelessness, inability to access healthcare and medication (21). Providing not only medical but also comprehensive psychosocial care is crucial when addressing medication regimen nonadherence as a cause of treatment failure.

Health Literacy Among the Older HIV Infected Population

Health literacy (HL) has also been identified as an important factor in the patient's management of disease. HL is the ability of a patient to obtain and understand basic medical information so they can make informed decisions surrounding their health care (29). Patients with lower HL have been found to have less knowledge regarding their medication names and purposes. This is directly correlated with poor clinical outcomes and a higher all-cause mortality rate. The literature shows that advancing age is associated with declining HL. Older individuals tend to have multiple comorbidities that need to be managed and coordinated among more than one provider. This may be even more difficult for older patients with HIV who have an increased rate of comorbidities as compared to their uninfected counterparts (30). This healthcare management becomes exponentially harder for those individuals who are then afflicted with poor HL.

In 2016, the US Department of Education's National Assessment of Adult Literacy found that the majority (59%) of adults 65 years of age or older had a basic or below basic HL (31). Lower HL among these older individuals was associated with being a minority, having lower educational attainment, reduced physical function/overall physical health, and poor working memory and cognitive function. About half of older individuals with HIV have an associated neurocognitive disorder (30). Worsening cognition may lead to the inability of an older individual to properly manage their acute and chronic medical problems. Inability to utilize preventive care due to inadequate HL has been associated

with increased emergency room visits, inpatient admissions, and overall increased usage of healthcare services. One study, examining expenditure of individuals enrolled in a Medicare managed care plan over a one year period, showed that those with poor HL acquired significantly higher medical expenses, including ER visits and inpatient admissions, as compared to individuals with suitable HL (32).

Multiple studies have shown lower HL is associated with medication nonadherence and worsening care in those with HIV (30). These individuals have a worse general understanding of their disease, treatment regimen, and prognosis if their HIV is left untreated (33). They are also more likely to have higher viral loads, lower CD4 cell counts, poorer health, and overall worse health outcomes as compared to HIV infected individuals with acceptable HL. Because health literacy plays such a vital role in effectively managing one's health, interventions have been sought out to improve healthcare delivery to those with low HL.

Screening tools have been evaluated and implemented to identify patients at risk of poor HL. Assessing a patient's education level can be an equally effective method of determining if a patient has limited HL (29). Technology continues to be developed to engage patients and effectively relay their health information. Embodied Conversational Agents (ECA) is an example of computer software that aims to bridge the gap between technology and low HL. ECA was found to be approachable and user-friendly by both patients with sufficient and insufficient health care literacy. Along with this technology to

deliver health information, tailoring healthcare education to the patient's individual needs has been associated with better health outcomes (30). This may include taking into consideration gender-specific needs, the mental health or cognitive functioning of the patient, and determining how much information is appropriate to deliver to the patient at one time.

Studies have shown it is important to limit medical jargon and keep language simple when discussing medical information with a patient. A team based approach, incorporating health care providers and other individuals with HIV, may benefit those with low HL when trying to improve management of their HIV and comorbidities. It is imperative that staff members who are involved in patientcare are properly trained on HL and how this affects patient health. Staff also needs to be given the proper tools and strategies to support those with poor HL so they can better advocate for their patient's care (30, 33).

In conjunction with these strategies, quantifying a patient's medication regimen complexity may be useful to optimize patient care and reduce adverse medical outcomes. Although the literature is inconsistent regarding the association between the MRCI and medication adherence, medication regimen complexity can be used as a tool to help identify those at risk of medication nonadherence.

Medication Regimen Complexity

The literature shows that reducing polypharmacy and the pill burden in the PLWH can result in better adherence to medications resulting in improvements in disease management and viral suppression (20, 27). In addition to the number of medications taken; dosage frequency, specific instructions surrounding medication administration, and the form in which the drug is taken has also been shown to affect adherence (34). Not until recently have researchers attempted to quantify medication regimen complexity. The Medication Regimen Complexity Index (MRCI) was created and validated based on medication dosage form, dosing frequency, and additional instructions given to individual medications (eg. break/crush tablet, dissolve tablet/powder, relation to food/liquid, etc.). All medications (prescribed and over the counter) can be factored into the MRCI. There is currently some evidence that increased total medication regimen complexity or burden is associated with decreased adherence (35). It is thought that the MRCI could be used as an adjunct tool, in addition to considering the many other factors discussed above, to help predict adherence. It has the potential to identify those at high risk for nonadherence offering an opportunity for the implementation of an appropriate intervention such as counseling, changing dosing frequency and/or the form of the prescribed medication.

The Antiretroviral Regimen Complexity Index (ARCI) was created to quantify regimen complexity for ARVs but it does not consider other medications patients with HIV may be taking (36). The ARCI is calculated in a similar fashion to the MRCI including number of pills, dosing frequency and form, special instructions, and necessary

preparations of the ARVs. The ARCI can also be used as a tool to better understand how complexity affects adherence and patient outcomes but it has some shortcomings. Some studies have shown increasing medication complexity with ARVs is specifically associated with decreased ARV adherence (35). One study compared the ARCI to the MRCI and found the mean complexity scores were not significantly different for ARV medications. The ARCI may not be as powerful of a tool because it does not consider non-ARV medications which can add substantial complexity to a patient's medication regimen. Further research needs to be performed to better identify the strength of MRCI as a predictor of medication adherence, which has implications for risk assessment and targeting interventions to improve patient's medical outcomes.

Chapter II. Manuscript

Title: Regimen Complexity in Aging HIV-Infected Veterans: Data from HAVACS

Authors: Daniel J Reichman, Jodie L Guest

Abstract:

Advances in antiretroviral (ARV) medication regimens have greatly contributed to the increased survival and subsequent aging of the population of persons living with HIV/AIDS (PLWHA). While the total daily pill burden for ARV and non-ARV medications has been examined by age in HIV-infected patients, regimen complexity is another aspect of polypharmacy that has been associated with adherence and clinical outcomes.

The HIV Atlanta VA Cohort Study (HAVACS) includes all HIV-infected veterans seen at the Atlanta VA Medical Center since 1982. The Medication Regimen Complexity Index (MRCI), developed by the University of Colorado Denver, was used to determine the complexity of a patient's medication process for a randomly selected subset of 146 patients prescribed medication and seen between January 1, 2004 - October 31, 2014. The MRCI score takes into account the route, dose, and frequency. The higher the MRCI scores, the greater the regimen complexity. Chi-square, Fischer's exact tests, and one-way analysis of variance were used to compare the MRCI score across age groups.

Patients were separated by age into three categories; Age Group 1: 23-44 years (mean 37) (n=47), Age Group 2: 45-55 years (mean 47) (n=50), and Age Group 3: 56-92 years (mean 63.6) (n=49). There was a statistically significant difference in MRCI mean score among the groups ($p<0.0001$). Mean MRCI scores by Age Group are: Group 1 mean score of 10.3, Group 2 mean score of 14.0 and Group 3 mean score of 20.9. Figure 1 shows the distribution of MRCI scores among the three age categories. Further analysis showed that there was a statistically significant difference in MRCI score means between Age Groups 1 and 3 ($p < 0.0001$) and Age Groups 2 and 3 ($p= 0.004$). The magnitude of the MRCI score varied significantly across the three age groups. Greater regimen complexity was seen with the oldest age group. Individually, age and regimen complexity have been associated with nonadherence. As PLWHA continue to age, measures of polypharmacy will be an essential component of clinical success.

Introduction:

Today, there are about 1.4 million people living with HIV (PLWH) in the United States (7). It is estimated that 50% of these individuals are over the age of 50 years old, which is expected to rise to 70% by the year 2030. Advances in antiretroviral (ARV) medication regimens have greatly contributed to the increased survival and subsequent aging of the PLWH. This aging population requires special attention in the management of their comorbid conditions. There are many disease processes that are more commonly seen among elderly groups such as hypertension, peripheral arterial disease, cardiac disease,

hepatic and renal insufficiency, and neurocognitive impairment (20-21). Due to these comorbidities, the older PLWH are at greater risk of polypharmacy and pill burden.

Polypharmacy, defined as taking five or more prescribed medications, has been associated with poorer health outcomes, greater likelihood of drug-drug interactions and nonadherence to medications (19, 21). Increasing pill burden can lead to increased frailty, disability, increased mortality, and increased risk of falls (23). ARVs have been found to interact with many medications more commonly used by the older population such as antihypertensives, statins, antiarrhythmics, anticoagulants, H2 blockers, antidepressants, antibiotics, steroids, and narcotics (24). Research has shown a clear association between polypharmacy and non-adherence (25). Ensuring patients can maintain adherence to their ARVs is critical for viral suppression and reduces the risk for viral resistance, opportunistic infections, and hospitalization (26). Current guidelines for the use of ARTs in HIV infected individuals focus on reducing pill burden and implementing once daily medication regimens with fewer side effects to help increase levels of adherence.

Regimen complexity is another contributor to polypharmacy that has been associated with adherence and clinical outcomes (34-35). The Medication Regimen Complexity Index (MRCI) was created and validated based on medication dosage form, dosing frequency, and additional instructions given to individual medications (eg. break/crush tablet, dissolve tablet/powder, relation to food/liquid, etc.). All medications, prescribed and over the counter, can be factored into the MRCI. It has the potential to identify those

at high risk for nonadherence so an appropriate intervention can be implemented such as counseling, changing dosing frequency or the form of the prescribed medication.

While the total daily pill burden for ARV and non-ARV medications has been examined by age in HIV-infected patients, our study aimed to examine the relationship of medication regimen complexity and age among a cohort of HIV positive patients from the HIV Atlanta VA Cohort Study (HAVACS).

Methods:

Data for this study was collected from The HIV Atlanta VA Cohort Study (HAVACS). Since 1982, data has been collected on all HIV-infected veterans seen at the Atlanta VA Medical Center (37). Currently, 4,334 patients have been entered into the database. There are many specific data points collected on patients including, but not limited to, birth, gender, race, mode of transmission, date of first positive HIV test, CD4+ cell count, plasma HIV-RNA level, AIDS and non-AIDS events, prophylaxis, antiretroviral data, and other laboratory and pharmaceutical data.

The Medication Regimen Complexity Index (MRCI) was developed by the University of Colorado Denver used to determine the difficulty of a patient's medication process (38). The MRCI considers the dosage form (oral, topical, inhaled, etc), dosing frequency, and

additional directions. Higher MRCI scores indicate greater regimen complexity. The MRCI Master Template is made available publicly by the University of Colorado (Appendix A). The purpose of our study was to determine the association between MRCI and age. This, along with additional analysis, was accomplished by analyzing the data from a randomly selected subset of 146 patients, from HAVACS, who were prescribed medication and seen from January 1, 2004 - October 31, 2014.

Data from HAVACS was cleaned and analyzed using statistical software. (SAS Institute, Inc. Cary NC) Descriptive statistical analysis was conducted on the variables detailed in Table 1. Univariate analysis was performed using SAS PROC MEANS and SAS PROC FREQ to determine patient demographics from 1,299 unique patients from HAVACS in 2014. The subset of 146 patients was separated into three similar sized groups based on age (<45 years, 45-55 years and >55 years). Fischer's exact tests, and one-way analysis of variance with post-hoc Tukey was performed using SAS PROC GLM to compare the continuous variable, MRCI score, across three categorical age groups. Similar analysis was performed to assess the ARV, non-ARV, and total daily pill burden across the three age groups. Statistical significance of results was performed at the $p=0.05$ significance level.

The distribution of MRCI score by age category and total daily pill burden by age category were examined using box and whisker plots (Figures 1 and 2).

Results:

Patient demographics were analyzed for 1,299 individuals of the HAVACS (Table 1). 1,255 (96.6%) of the subjects were male. 1,047 (80.7%) of the patients were non-Hispanic Blacks; 240 (18.5%) subjects were non-Hispanic Whites; 10 patients (0.8%) were Hispanic; and one patient was Other (0.1%). The mean age of the cohort was 54.4 (standard deviation (SD) 9.5) years old. Patient medical history was also recorded in Table 1. 743 (58.8%) subjects had a CD4 cell count of less than 200 cells/mm^3. 360 (28.5%) of the individuals in the study had a CD4 cell count between 200 and 350 cells/mm^3. 161 (12.7%) subjects had a CD4 cell count of over 250 cells/mm^3. HIV risk factor information was collected from individuals in this study. Six hundred sixty-two patients (51.8%) of the cohort were labeled as MSM, 152 (11.9%) were considered IDUs, 90 (7.1%) were reported as high-risk heterosexuals, 362 (28.4%) patients had unknown HIV risk factors, and 11 (0.9%) individuals had Other HIV risk factors. 849 (65.4%) of the patients in HAVACS had an HIV infection which progressed into an AIDS diagnosis. 315 (24.3%) individuals had a Hepatitis C comorbidity. The mean age in which patients were diagnosed with HIV was 37.7 (SD 9.2) years old. Of the 849 patients who were diagnosed with AIDS, the mean age of diagnosis was 44.2 (SD 9.4) years old. The median number of pills taken per individual in their current medication regimen was 7 (4,12).

Patients were separated by age into three categories/groups, ranging from the youngest patients to the oldest. The first age category (N=47) had a mean age of 37 years old with a range from 23 to 44. The second category (N=50) had a mean age of 50.3 with a range from 45 to 55 and the third age category (N=49) had a mean age of 63.6 with a range from 56 to 92. Initial analysis showed there was a statistically significant difference in MRCI mean score among the three groups ($F=10.12$, $p<0.0001$). Group one had a mean score of 10.3 (SD 7.9), group two had a mean score of 14.0 (SD 11.0) and group three had a mean score of 20.9 (SD 14.9). Figure 1 shows the distribution of MRCI scores among the three age categories.

Further analysis showed the difference in mean MRCI scores between groups one and three was 10.6 ($p < 0.0001$, 95% CI: 4.89, 16.20) and the difference between groups two and three was 6.9 ($p= 0.004$, 95% CI: 1.33, 12.47). The differences between mean MRCI scores were both statistically significant at the 5% significance level (Table 2).

When evaluating whether the number of pills taken per person increased with age, initial analysis showed there was a statistically significant difference in number of pills taken among the three groups ($F=11.77$, $p<0.0001$). The mean number of pills taken per person in group one was 4.23 (SD 3.23); group two took an average of 5.94 pills (SD 4.01); and group three took an average of 8.55 pills (SD 5.59). Figure 2 shows the distribution of pills taken among the three age categories. Analysis showed the difference in the mean number of pills taken between groups one and three was 4.3 ($p<0.0001$, 95% CI: 2.19,

6.44) and the difference between groups two and three was 2.6 (p= 0.004, 95% CI: 0.52, 4.70). The differences in mean number of pills taken between these groups were both statistically significant at the 5% significance level (Table 2).

Pills taken by patients in this study were further separated into ARV and non-ARV medications. There was a statistically significant difference in the number of ARV and non-ARV medications taken daily among the three age groups (F= 4.12, p = 0.0183; F=5.83, p= 0.0037). Table 2 shows the mean ARV daily pill burden for group one was 1.8 (SD 1.5), group one was 2.3 (SD 2.0), and group three was 2.8 (SD 1.9). The non-ARV daily pill burden for group one was 3.3 (SD 4.0), group two was 5.7 (SD 5.8), and group three was 7.2 (SD 7.0).

The difference in the ARV daily pill burden between groups one and three was 1.0 (p= 0.0047, 95% CI: 0.1832, 1.9175). The difference in the non-ARV daily pill burden between groups one and three was 3.9 (p= 0.0009, 95% CI: 1.194, 6.738). Both differences were found to be statistically significant at the 5% significance level.

Discussion:

It has been well established that the aging PLWH population is at greater risk of polypharmacy and pill burden which can lead to adverse health events and nonadherence

to their medication regimen and treatment failure (18, 23, 25-26). While the total daily pill burden for ARV and non-ARV medications has been examined by age in HIV-infected patients, regimen complexity is another contributor to polypharmacy that has been associated with adherence and clinical outcomes. Our study aimed to elucidate how the MRCI is associated with age among a cohort of HIV positive individuals from HAVACS.

Our study found that the MRCI increases with age with the largest difference in MRCI observed between the youngest group (age < 45 years) and the oldest group (age > 55 years). This study also supports the literature showing the older HIV positive population is subject to higher total pill burden. Older individuals tend to have more comorbidities necessitating careful medical management. Research has shown that older patients with HIV are at a greater risk of polypharmacy due to their comorbidities in addition to their HIV (18). Our results support this finding in that the oldest group of individuals had a higher non-ARV daily pull burden. The relationship between the daily burden of ARVs and age has not been well studied, but our results suggest individuals older than 55 take more ARV medications as compared to those less than 45 years old.

This study demonstrates that both MRCI and total pill burden increases with age. This is significant because increasing MRCI and polypharmacy, independently, have been associated with nonadherence (24, 34-35). Polypharmacy is related to poorer health outcomes in the older population and drug-drug interactions. Ensuring patients can

maintain adherence to their ARVs is critical for viral suppression and reduces the risk for viral resistance, opportunistic infections, and hospitalization. Studies have shown that taking simpler or single tablet ARV medication regimens results in better adherence, lower risk of hospitalization and longer time to hospitalization as compared to patient taking a multiple tablet regimen (20, 27).

In addition to pill burden and complexity of prescription regimen, there are many other factors that contribute to patient adherence to their ART. Other issues to consider include mental illness including depression, neurocognitive impairment, limited social support, substance abuse, homelessness, inability to access healthcare and medication, health literacy (HL) (20). Providing not only medical care but also comprehensive psychosocial care is crucial when addressing medication regimen nonadherence as a cause of treatment failure. MRCI can be used in conjunction with tools that exist to identify individuals with poor HL and thus greater risk for non-adherence and adverse health outcomes.

Strengths and Limitations

This is one of the first studies to examine the relationship between MRCI and age among a cohort of HIV positive patients. It has been established that older individuals have a more complex medication regimens. This study suggests older HIV positive individuals may be a good population to target with regard to interventions that might prevent medication nonadherence. The research presented further confirms that older PLWH are

at higher risk for polypharmacy given the likelihood of having a higher number of comorbidities that require medical management. This study provides a stepping-stone for future research, which may further elucidate how MRCI, age, nonadherence, and patient outcomes are associated. Determining how the MRCI can be used as a tool to identify those at risk of nonadherence can help guide appropriate interventions and significantly contribute to the improvement of patient outcomes.

There are some limitations that exist including the study size (n=146). This small sample size provides less statistical power and, although, we could reject the null hypothesis that there was no difference in MRCI between the three age groups, a larger sample size would allow us to do this with more certainty. Results from this study, including patient demographics, can be generalized to the HIV positive cohort of persons who receive care at the Veterans Affairs in Atlanta, GA, but lacks generalizability to other HIV populations. The patients in this study were 96.6% male, 80.7% non-Hispanic Black, and over half were men who have sex with men. The results from this study can only be generalized to the entire cohort of HAVACS. Calculating the MRCI is performed using a validated spreadsheet for each individual patient. Although there are guidelines for its use, there is no formal training for its use and its complexity may lend itself to user error. Reproduction of results is essential to confirm internal validity.

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Tables

Table 1. Patient Demographics and Medical History among HIV-Positive Patients from the HIV Atlanta VA Cohort Study (HAVACS)

Characteristic		**Overall n=1,299**
Patient Demographics	**n**	**%**
Male	1,255	96.6
Race/Ethnicity[a]		
Non-Hispanic White	240	18.5
Non-Hispanic Black	1047	80.7
Hispanic	10	0.8
Other	1	0.1
	Mean	Std Dev
Age (years)	54.4	9.5
Patient Medical History	**n**	**%**
Nadir CD4 Cell Count (cells/mm^3)[b]		
<200	743	58.8
200-350	360	28.5
>350	161	12.7
HIV Risk Factors[c]		
Men who have sex with other men (MSM)	662	51.8
Intravenous Drug User (IDU)	152	11.9
High risk heterosexuals	90	7.1
Unknown	362	28.4
Other	11	0.9
AIDS Diagnosis	849	65.4
Hepatitis C Comorbidity	315	24.3
	Mean	Std Dev
Age (years) at HIV diagnosis[d]	37.7	9.2
Age (years) at AIDS diagnosis (n=849)	44.2	9.4
Number of Pills Taken	7[e]	4,12[f]

[a]1 missing observation
[b]35 missing observations
[c]22 missing observations
[d]7 missing observations
[e]Median number of pills taken
[f]Q1, Q3 number of pills taken

Table 2. MRCI Scores by Age Group, 2014[a]

Characteristic	<45 years (n=47)	45-55 years (n=50)	>55 years (n=49)	P-value
Patient age, mean	37.0	50.3	63.6	-
MRCI score, mean (SD)	10.3 (7.9)	14.0 (11.0)	20.9 (14.9)	<0.0001
ARV daily pill burden, mean (SD)	1.8 (1.5)	2.3 (2.0)	2.8 (1.9)	0.0183
Non-ARV daily pill burden, mean (SD)	3.3 (4.0)	5.7 (5.8)	7.2 (7.0)	0.0037
Total daily pill burden, mean (SD)	4.2 (3.2)	5.9 (4.0)	8.6 (5.6)	<0.0001

[a]Values reported represent the mean and standard deviation (SD) for 146 randomly selected patients who were seen for care and prescribed medication at AVAMC from January 1, 2014 through October 31, 2014

Figures

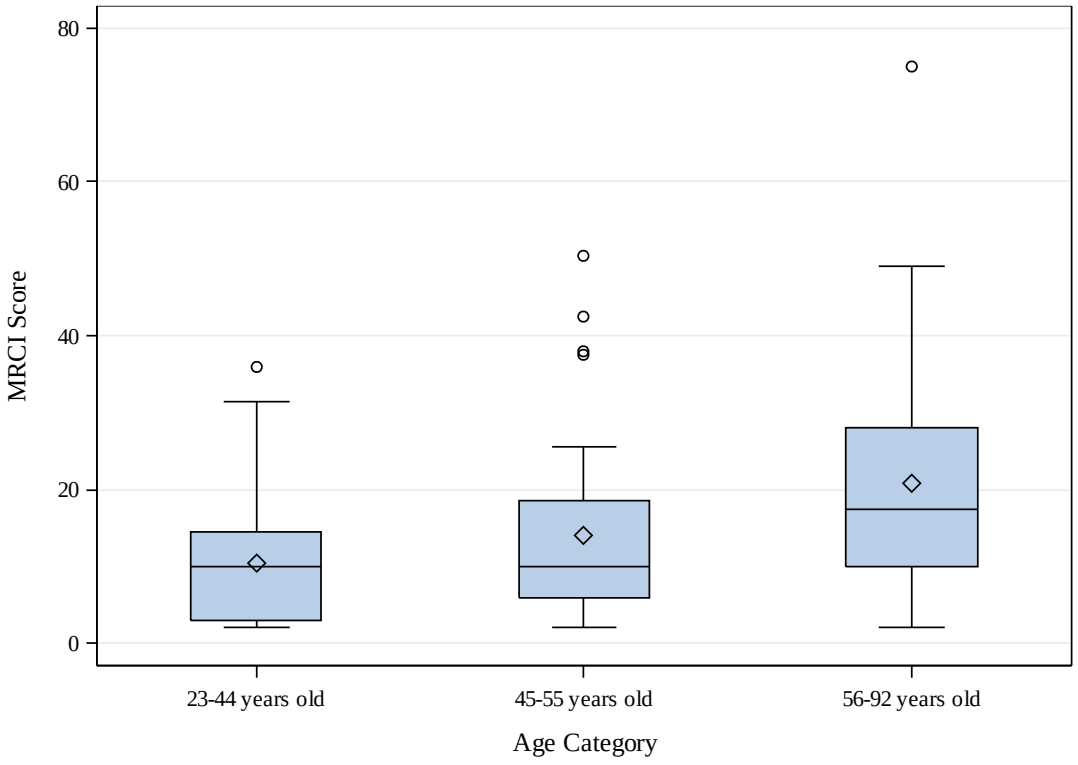

Figure 1. The distribution of Medication Regimen Complexity Index score by age category. Category 1 (N=47) has a mean score of 10.3 (sd= 7.9); Category 2 (N=50) has a mean score of 14.0 (sd= 11.0); Category 3 (N=49) has a mean score of 20.9 (sd= 14.9).

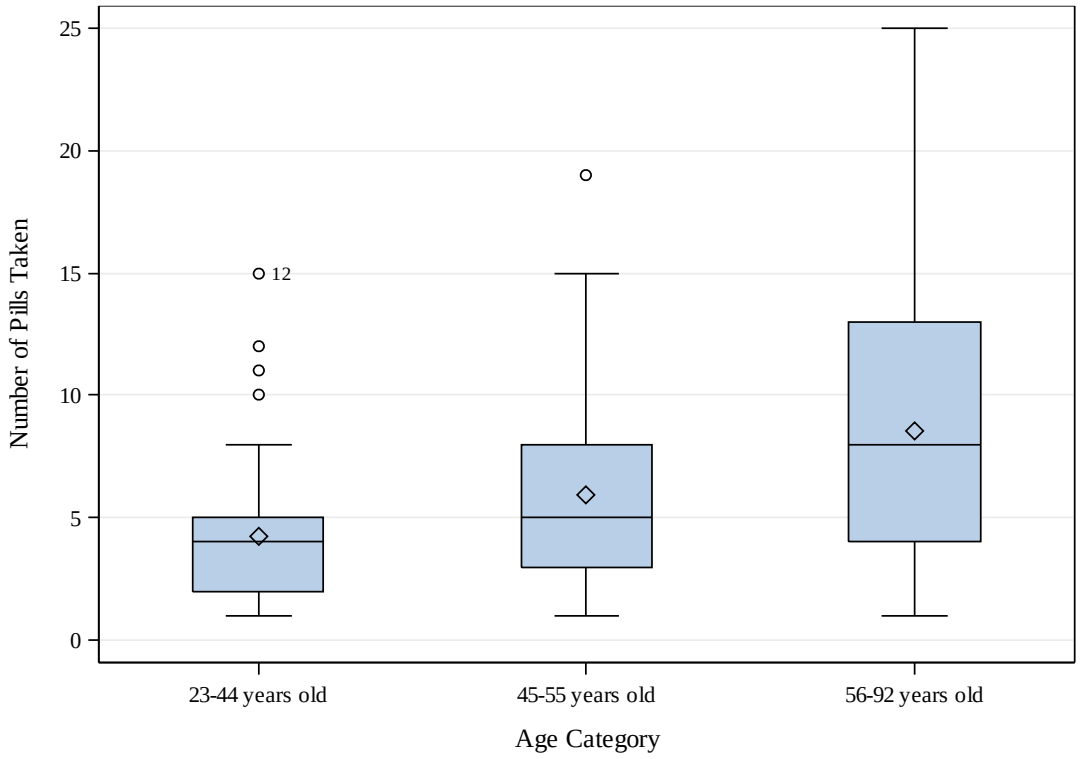

Figure 2. The distribution of Number of Pills Taken Daily by age category. Category 1 (N=47) has a mean score of 4.2 (sd= 3.2); Category 2 (N=50) has a mean score of 5.9 (sd= 4.0); Category 3 (N=49) has a mean score of 8.6 (sd= 5.6).

Chapter III. Summary, Public Health Implications, Possible Future Directions

Summary

The intent of this study was to examine the relationship between the MRCI and age from a subset of individuals in HAVACS. Patient data analyzed from HAVACS includes all HIV-infected veterans seen at the Atlanta VA Medical Center since 1982. The MRCI for each patient was calculated using a tool developed by the University of Colorado, which takes into account the form of medication taken, dosing frequency and additional directions necessary for medication use. Our research showed that MRCI increases with a patient's age. The largest difference in MRCI was observed between patients less than 45 years old and those greater than 55 years old. Secondary analysis showed that ARV, non-ARV, and total pill burden all increased with age. The largest difference in burdens for all three categories were observed between the groups less than 45 years old and greater than 45 years old.

This is one of the first studies to examine the association between MRCI and age among a group of HIV infected individuals. According to the previous body of literature, older patients with HIV have increased rates of polypharmacy, which is related to worse health outcomes (22). Older patients with HIV have more comorbidities compared to their non-HIV infected counterparts necessitating medical management (18). Our research supports this finding in that the oldest group of patients (>55 years old) had higher rates of all forms of pill burden as compared to the youngest group (<45 years old). The relationship

between the daily burden of ARVs and age has not been well studied, but our results suggest individuals older than 55 take more ARV medications as compared to those less than 45 years old. The results found from this study help support the idea that MRCI and polypharmacy both contribute to nonadherence and worsening health outcomes for which PLWH are at a greater risk.

Public Health Implications

This study showed that MRCI and all forms of pill burden was greatest for the oldest population in our study (>55 years old). Where there have been many studies to show that polypharmacy impacts adherence and patient outcomes, there has not been a lot of research on MRCI, adherence, and health events (22). Some studies support that increased MRCI is associated with decreased adherence (35). The literature has shown that decreasing polypharmacy and making medication regimens simpler can help improve adherence resulting in better disease management and lower the risk of hospitalization (20, 27). The older HIV infected individuals, who are more likely to have a higher MRCI, are also at risk for decreased adherence. Using the MRCI in conjunction with assessing for polypharmacy can help identify patients who are at risk for nonadherence and worse health outcomes. When a patient is identified using these tools, an appropriate intervention can be implemented such as counseling, changing dosing frequency or the form of the prescribed medication.

In addition to pill burden and complexity of prescription regimen, many other factors contribute to patient adherence to ART. Other factors include mental illness including depression, neurocognitive impairment, limited social support, substance abuse, homelessness, inability to access healthcare and medication, and health literacy (HL) (20). Older individuals have higher rates of low HL (31). Older individuals with poor HL are more likely to have higher viral loads, lower CD4 cell counts, poorer health, and overall worse health outcomes (33). Existing tools can be used to identify those at risk of poor HL so that techniques can be used to ensure the effective delivery of health information to these patients. In conjunction with these strategies, quantifying a patient's medication regimen complexity and reducing polypharmacy may be useful to optimize patient care and reduce adverse medical outcomes.

Possible Future Directions

Future studies should seek to better elucidate the relationship better MRCI and adherence, as the current literature is somewhat controversial. Studies can be stratified by age to help identify a population at greater risk. MRCI and viral load, hospitalizations, adverse health events, and mortality should be more closely examined to better understand the how the MRCI can be used as a predictive tool of certain health outcomes. Further research needs to be done to determine how the MRCI can be made more user-friendly for use as a clinical tool. Development of a MRCI "cut-off" value would be helpful when providing patient education. The ability to explain to patients, with a score greater than a determined and validated value, gives them a higher likelihood for

worsening adherence and poorer health outcomes would be of tremendous value during an office visit in helping to promote medication compliance.

Appendix A

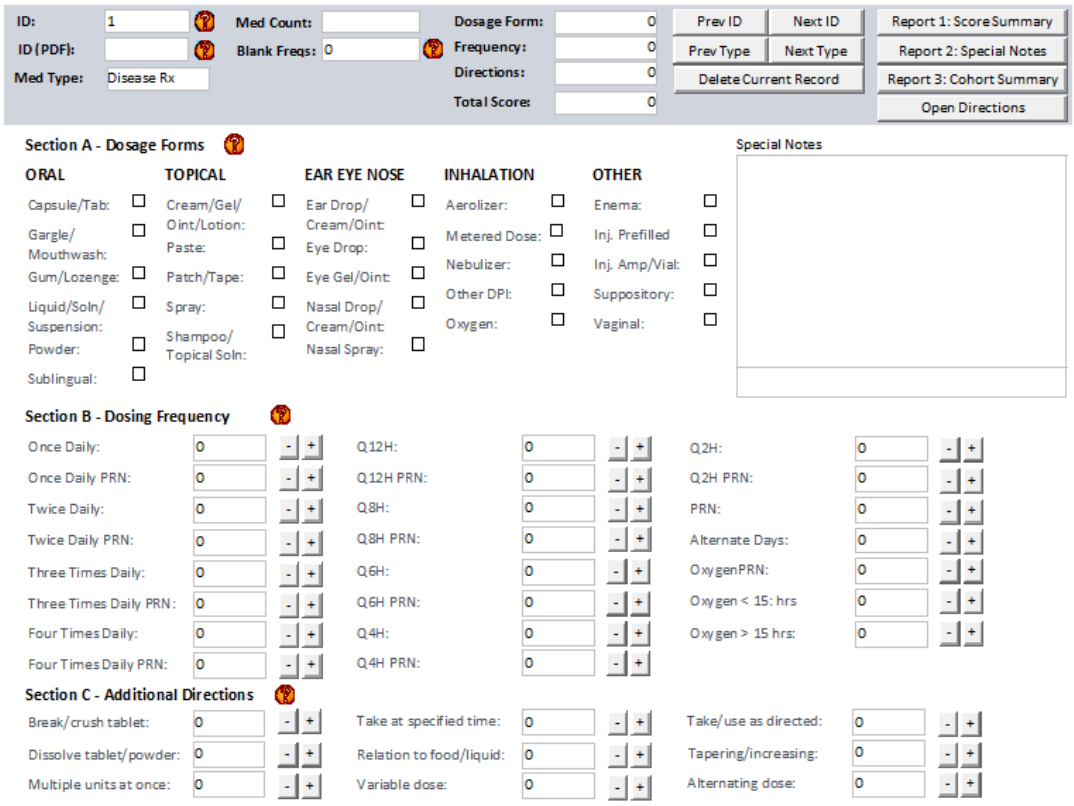

Figure A1. Screen shot of MRCI Master Template