Review

Drug-drug interactions in ageing HIV-infected individuals

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The effectiveness of antiretroviral therapy has significantly improved life expectancy of HIV-infected individuals. Global campaigns and awareness programmes have led to substantial drop in the rate of new infections. Consequently, the proportion of ageing HIV-infected individuals continues to increase. HIV-associated and age-related comorbidity necessitates polypharmacy in ageing individuals living with HIV/AIDS. The risk of drug-drug interaction increases with the number of administered drugs. Age-related changes in the body physiology are known to influence pharmacokinetic and pharmacodynamic profile of administered drugs. These changes include reduction in blood flow to major organs, decline in metabolic activities, body mass shrinking and changes in body water and fat proportion. These factors contribute to the perceived and reported higher incidence of drug-drug interaction in this population. The current paper reviews the reported incidence of drug-drug interactions in ageing HIV-infected individuals, providing relative mechanisms and possible factors responsible in comparison to younger population. Health professionals should be aware of the drug interaction risks involved in the management of HIV/AIDS in the ageing population; be able to anticipate them based on concomitant medications and manage them as necessary.

Key words: Drug-drug interaction, drug metabolism, drugs, ageing, HIV/AIDS, cytochrome P450.

INTRODUCTION

Since the advent of highly active antiretroviral therapy (HAART) in 1990s, the management of HIV has resulted in improved quality of life, survival and life expectancy of infected individuals (Antiretroviral Therapy Cohort Collaboration, 2008; van Sighem et al., 2010; Mills et al., 2011; Nakagawa et al., 2012). Although without a cure, HIV infection with early diagnosis and treatment adherence has become a chronic disease albeit life-threatening. Formerly considered the disease of the young people, HIV infection in ageing individuals is gaining prominence as the number of affected people continues to increase (Grabar et al., 2006). However, there are no specific guidelines targeted at drug management of HIV in older patients. Information on the safety and efficacy of current antiretroviral (ARV) regimen in older patients are not sufficiently available. Clinical trials have often excluded older individuals until recently (Limb, 2011). Meanwhile, little research has been done to assess the impact of ageing on the disease. Available literature indicates that the ageing population may be more vulnerable to certain complications arising from drug therapy and comorbidity (Mallet et al., 2007).

The consumption of multiple therapeutic agents often results in serious drug-drug interactions (DDIs), which have been shown to account for 3-5% of all in-hospital medication errors (Leape et al., 1995; Obreli-Neto et al., 2012). The phenomenon is of greater concern in the elderly patients, especially those who are on antiretroviral therapy (ART) (Derek and Philips, 2009). The consequence of clinically significant DDIs is enormous. These may include toxicity, treatment failure, organ

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Abbreviations: ART, Antiretroviral therapy; ARV, antiretroviral; CYP, cytochrome P450; DDI, drug-drug interaction; HAART, highly active antiretroviral therapy; NNRTI, non-nucleotide reverse transcriptase inhibitors; NRTI, nucleotide reverse transcriptase inhibitors; PI, protease inhibitors; US CDC, United States Centre for Disease Control and Prevention.
damage, increased mortality and/or development of viral resistance to ART (Clarke et al., 2008). ART and its associated complications in ageing individuals will continue to present challenges to healthcare providers.

Aim, search strategy and selection criteria

The current review was aimed at providing an overview of reported incidences of drug-drug interaction in ageing individuals (50 years and above). Although, definitions of old age vary, a study to evaluate the effects of age on HIV prognosis identified age 50 as a determining factor affecting the course of clinical progression of infection to AIDS and death (Egger et al. 2002; Nogueras et al., 2006). This age benchmark is used by the World Health Organization (WHO) and the US Centre for Disease Control and prevention (CDC). This paper also provides concise review of the known factors that play significant roles in the perceived and reported higher incidences of drug-drug interaction in ageing individuals. The review was systematically conducted by searching the databases of PUBMED (National Center for Biotechnology Information), EMBASE and COCHRANE libraries for original researches, case reports and other relevant publications on drug-drug interaction in ageing HIV-infected individuals. The search terms used include the following and the combination thereof: “adverse drug reaction”, “aged”, “aging”, “antiretroviral drugs”, “antiretroviral therapy”, “cytochromes”, “drug interactions”, “drug-drug interactions”, “drug metabolism”, “elderly”, “HIV/AIDS”, “pharmacokinetics”, “pharmacodynamics”. Further searches were performed with the combination of the individual antiretroviral drugs and the above search terms. The reference lists in the identified articles were manually searched for relevant publications. Searches were not limited by date or place of publications, but to publications available (originally or translated) in English language.

EPIDEMIOLOGY OF HIV/AIDS IN AGEING POPULATION

Figures from the US CDC indicated that 29% of people living with HIV in the United States were aged 50 years and older, as at 2005. Data from sub-Saharan Africa as at 2007 indicates that an estimated 3 million people aged 50 and above were living with HIV with a prevalence of 4.0%, compared with 5.0% among those aged 15 - 49 years (Negin and Cumming, 2010). In a cohort study of 660 HIV diagnoses in England, 3% were aged 60 years and over with 44% of these diagnosed after the age of 60 (Pratt et al., 2010). The most recent HIV/AIDS statistics as released by the UNAIDS in 2011 shows that new HIV infections are declining. According to the release, there were an estimated 2.7 million people who became newly infected with HIV in 2010, which was about 15% less than the figure in 2001, and more than 21% below the number of new infections at the peak of the epidemic in 1997. Over 700 000 AIDS-related deaths were averted in 2010 alone according to the global report. Thus, there is increasing proportion of ageing HIV-infected individuals.

Reduced HIV/AIDS mortality due to the efficacy of ART has been identified as one of the various factors responsible for the growing proportion of ageing HIV-infected individuals (Antiretroviral Cohort Collaboration, 2008). Fewer preventive education and campaign programs targeted at this population group as compared to younger individuals and late diagnosis have also been identified (Orel et al., 2005). Although older people have been stereotyped to be less sexually active, studies have found that up to 81.5% individuals aged 50 and above are sexually active, including prostitution (Gott, 2001; Schick et al., 2010), and this increases the number of new infections in this group. A risk assessment placed older women at higher risk of infection due to age-related vaginal thinning, dryness and ease of vaginal wall tears (Coleman, 2003). Surveys have also found that a high majority of sexually active individuals 65 years and older do not use condom consistently even with multiple partners (Leigh et al., 1993; Odor et al., 2011). Another contributor is injection drug usage, which accounts for more than 16% of all HIV transmission in individuals 50 years and older (Linsk, 2000; Youmans et al., 2011). According to projections, more than half of all HIV-infected individuals will be ≥50 years of age by 2015 (Effros et al., 2008; Negin and Cumming, 2010).

RELEVANT MECHANISM OF DDI IN AGEING HIV-INFECTED INDIVIDUALS

Various studies have reported the pharmacokinetic and pharmacodynamic of DDIs in ART. Pharmacokinetic interaction usually results from the modification of the absorption, distribution, metabolism and/or excretion of one drug induced by another leading to alteration of the effective concentration of active drugs in the body (Dresser et al., 2000; Piscitelli and Galliano, 2001; Rolan and Molnar, 2007). Pharmacodynamic drug interaction occurs when the pharmacological effect of one drug is influenced by the presence of the other by way of addition, antagonism or synergy.

Alteration in oral drug absorption

Current guidelines on ART rely exclusively on oral drug administration. Thus, drug-induced physiological and biochemical changes in the gastrointestinal tract (GIT) can modify drug absorption patterns. For example, opioids and drugs with anticholinergic properties can increase GIT transit time, leading to delayed absorption and onset of systemic action of co-administered drugs. Slow gastrointestinal motility can also accelerate pre-systemic degradation of drug substrates (e.g. levodopa)
of various intestinal enzymes. Cholinomimetic drugs like metoclopramide and loperamide increase gastric emptying and GIT motility, which can lead to a fluctuating contact between the drug molecule and the absorbing sites. In addition to the alteration in the drug absorption, this can lead to changes in the pharmacological effect of the drug (Wadhwa et al., 1987; Kuo et al., 2010).

The physicochemical properties of some drugs can alter gastrointestinal pH and influence the ionization, disintegration and dissolution of co-administered drugs (de Castro et al., 1996; Yang et al., 2012). Such instance can lead to erratic absorption behaviour of pH-sensitive drugs like furosemide and triazolam. The absorption of weak bases like albuterol, allopurinol, diazepam, diphenhydramine, metoprolol and morphine can be significantly affected by increased gastric pH. Enteric coated drugs may dissolve in altered gastric pH (Krishna et al., 2009). Gastrointestinal drug-drug complexation can affect the effective concentration of absorbable drugs. An example is the well-known binding of tetracycline and polyvalent metal-containing antacids leading to poor tetracycline absorption. Changes in the gastrointestinal pH in the presence of antacids can also influence the absorption of a number of drugs including aspirin, ciprofloxacin and digoxin. The inhibition/induction of intestinal pre-systemic metabolism is also another common DDI that can influence systemic drug bioavailability (Dressman et al., 1993; Choi et al., 2010).

Changes in drug distribution

Alteration in protein binding of one drug by another can alter the effective concentration and pharmacological activity (Keller et al., 1984; Yoon et al., 2011). This can be as a result of competitive inhibition of protein binding by drug substrates and/or displacement form binding sites, leading to changes in the bound and unbound fraction. This type of DDI is of clinical significance only with drugs with narrow therapeutic range, or steep concentration (of unbound fraction)-effect profile, higher (>85%) protein binding and relatively low volume of distribution (DeVane, 2002; Takizawa et al., 2006). Two of the most commonly used drugs in elderly patients are warfarin and aspirin. Warfarin is highly protein bound and has a narrow therapeutic margin. Aspirin, when combined with warfarin can increase the free fraction of warfarin, thereby predisposing to higher risk of prolonged bleeding (Chan, 1995; Harder and Thürmann, 1996; Zhou et al., 2012). The antimalarial drug, atovaquone has been shown to interact with warfarin probably through the displacement from binding sites (Hidalgo et al., 2011).

Alteration in drug metabolism and transport

The involvement of cytochrome P450 (CYP), phase II metabolic enzymes and transport proteins in pharmacokinetic DDI has been detailed in various publications (Shitara et al., 2003; Müller and Fromm, 2011). The major isoforms of CYP involved in drug metabolism are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. CYP3A4 is responsible for the metabolism of more than 50% of CYP-mediated drug metabolism, while CYP2D6 accounts for about 25%. Decline in liver function associated with age has been reported to affect CYP expression. It has been shown that hepatic CYP3A4 activity declines by 8% per decade in older adults (Chapron, 2001; Shitara et al. 2005; Kiang et al., 2005; Han, 2011). Hepatic diseases which are common in ageing population are a factor that can affect the expression and function of hepatic CYP and transport proteins. Decline in hormonal activities and poor nutrition in ageing individuals can influence the expression of these enzymes.

The inhibition and/or induction of CYP and transport proteins are the major mechanism for pharmacokinetic DDI, and earlier published works have detailed this (Dresser et al., 2000; Lee et al., 2012). The knowledge of the specific CYP isozymes involved in the metabolism of individual drugs makes the prediction of DDI possible following concurrent administration. Notable example of the beneficial application of CYP inhibition is the use of ritonavir, a CYP3A4 inhibitor, to enhance the oral bioavailability of saquinavir and other CYP3A4 substrates used in ART in what is called ritonavir boosting. Guidelines for effective ART recommend the ritonavir boosting as part of PI-based regimen for treatment naïve patients (Hammer et al., 2006). Current ART regimen includes at least 3 drugs from preferably 2 different classes.

There are six major classes of drugs approved by the US-FDA for the treatment of HIV/AIDS, which include nucleotide reverse transcriptase inhibitors (NRTI), non-nucleotide reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors, integrase inhibitors, and chemochin receptor CCR5 antagonists. The PIs are the most potent ARVs and are often used in combination with other ARVs. They interact with infective viral proteins, preventing the cleavage of the core viral protein leading to the loss of viral infectivity (Fernández-Montero et al., 2009).

The NRTIs competitively inhibit the viral reverse transcriptase enzyme, thereby preventing the formation of the viral protein. This process inhibits viral replication. With the exception of abacavir, all the NRTIs are eliminated primarily by the kidneys and are not involved in the CYP-mediated DDIs (Pilliero, 2004; Bonora et al., 2006; Bazzoli et al., 2010). Fusion inhibitors which include enfuvirtide prevent HIV infection by blocking the fusion of the virus with the host cell at the initial point of contact. The metabolism of enfuvirtide is not CYP-dependent and its effect on CYP-mediated metabolism is minimal (Zhang et al., 2004). Entry inhibitor, maraviroc, blocks the cell-surface co-receptor CCR5, thereby inhibiting viral entry into the host cell. It is a CYP3A4
substrate making it a potential candidate for CYP-induced DDI (Hyland et al., 2008). Raltegravir is an example of integrase inhibitors. They protect against infection by preventing the integration of the viral DNA into the host cell. Integrase inhibitors are not substrates or inhibitors of CYP but principally metabolized by uridine diphosphate glucuronosyltransferase 1A1 (Iwamoto et al., 2008; 2009). Protease inhibitors (PIs) are known inhibitors and substrates to both CYP3A4 and p-glycoprotein. The most potent inhibitors in decreasing order are ritonavir, indinavir, nelfinavir, amprenavir and saquinavir (Hsu et al., 1998). Other enzymes involved in the metabolism of PIs are CYP2C19, 2D6, 2C9 and 2E1. There are currently 4 NNRTIs available. Of these, nevirapine and etravirine are substrates as well as inducers of CYP3A4. Delavirdine is a substrate and inhibitor of CYP3A4, while etravirine inhibits CYP2C9 and CYP2C19. Efavirenz induces and inhibits CYP3A isoforms, induction being more prominent (Smith et al., 2001; Ma et al., 2005). Thus, NNRTIs, PIs and maraviroc by virtue of their metabolic routes, are the most probable candidates for pharmacokinetic DDIs with other CYP substrates and/or inhibitors even among ARVs.

In a recent publication, Rawizza and Sax (2008) reported 3 clinically significant pharmacokinetic DDIs in patients with ritonavir-boosted darunavir (a relatively new PI) and an NNRTI regimen. Patients had infection for 15 years on average, at least 5 years of virological failure on a PI-containing regimen and an extensive genotypic evidence of PI and NRTI resistance. In large cohort study to assess the prevalence of the potential for DDI involving ARV in Kenya by Kigen and co-workers (2011), 1 in 3 patients on ARV drugs was found to be at the risk of clinically significant DDI. It underscores the reality of serious pharmacokinetic interactions among the various ARVs. The anticipation and management of DDI is one of the major challenges of ART optimization (Young, 2005; Robertson et al., 2007).

### Altered renal elimination

The kidneys are the major sites for the excretion of drugs and their metabolites. This is done through glomerular filtration and active tubular secretion. Glomerular filtration rate declines with age (Musso et al., 2011). The declining glomerular function can potentiate DDI, especially with the presence of aminoglycosides and other nephrotoxic drugs; diuretics and drugs that are systemically cleared predominantly by glomerular filtration (Bonate et al., 1998). There is a potential for DDI when two or more drug molecules compete for the same tubular secretion sites. For instance studies have reported DDI between NSAIDS, uricosuric drugs, penicillin and methotrexate (Iven and Brasch, 1988; Pea, 2005; Uwai et al., 2011). Change in the pH of urine is known to influence drug elimination. Acidified urine decreases the excretion of drugs that are weak acids; similar effect is observed with weak bases in alkaline (Madan, 1977). DDI can result from drug-induced modification of urine pH. In the elderly individuals, DDI resulting from declining renal functions is clinically significant for drugs like digoxin, which are primarily eliminated through the kidneys, and have narrow therapeutic margins.

### Pharmacodynamic interactions

A pharmacodynamic interaction is believed to be more common in the elderly population (Sera and McPherson, 2012). This is due to the often complex nature of their pathology and the high number of drugs consumed. Pharmacodynamic interactions alter the pharmacologic effects of the administered drugs by way of potentiation, antagonistic or additive effects. In clinical practice, the beneficial effect of pharmacodynamic synergy, potentiation and/or addition is often employed in chemotherapy and the drug management of various other medical conditions, including diabetes and cardiovascular disorders. A typical example of this application is the combination of ARVs from different classes to increase the antiviral potency of the regimen. The occurrence of undesirable synergy can lead to hypoglycaemic coma in diabetic patients or hypovolaemic shock in patients on diuretics. Some antipsychotic drugs may potentiate or augment anti-hypertensive, lower seizure threshold and may lead to glucose intolerance. The effects on the concurrent medications for these medical conditions can be deleterious. Antihistamines like diphenhydramine can synergise with sedatives, may cause confusion and delirium in the elderly when used in combination with anticholinergics, may worsen the symptoms of prostatic hypertrophy, may cause xerostomia, and may antagonize the effects of drugs used in Alzheimer’s disease. Efavirenz is known to exert effects on the central nervous system, and thus may impair co-medications for psychiatric disorders in HIV patients (Strehlau et al., 2011).

### WHY OLDER PATIENTS ARE AT GREATER RISK OF DDI

Compared with younger individuals, and age-matched uninfected persons, HIV-infected people of ≥50 years of age have a higher potential for pharmacokinetic and pharmacodynamic DDIs due to a number of factors often related to ageing physiology and drug use patterns.

### Ageing physiology and drug response in the elderly

The involution of thymus, the organ responsible for T-cell differentiation, increases with age (Aspinall and Andrew,
This age-related thymic atrophy (shrinkage from 70 g in infants to 3 g in the 70-year-old) is characterized by the replacement of thymopoietic with fatty tissue, leading to reduction in thymopoietic activities (Kuby et al., 2000). While HIV-1 infection is characterized by loss of naïve CD4\(^+\) T cells, dysfunctional CD4\(^+\) T cells increase with age (Bazdar et al., 2009). The influence of ageing on the immune system has thus, been shown to be responsible for faster disease progression in the elderly compared to HIV-infected young individuals (Effros, 2000). This faster progression and its associated comorbidity often necessitate earlier commencement of pharmacotherapy. DDI and its effects may be grossly exaggerated in ageing individuals due to frailty and ageing physiology. Ageing impairs both renal elimination and liver metabolism of drugs in most elderly patients. This may also apply to renal elimination due to declining renal function especially in individuals over 65 years old. These age-related changes are responsible for the known exaggerated effects of drugs in older people which are often seen as adverse drug reactions (Feely and Coakley, 1990).

One of the most important factors that affect drug response in the ageing population is the changes in the liver (Wilkinson, 2005). There is reduction in the size of the liver, decreased hepatic blood flow, and diminished expression and activity of metabolic enzymes (Iber et al., 1994; Sotaniemi et al., 1997). These factors affect the delivery of drug to the liver, to the metabolic enzymes, and the binding and distribution to other tissue spaces. The metabolism of drugs with high hepatic extraction \((E_H>0.7)\) whose systemic clearance is flow-dependent may significantly decrease consequent to reduced liver size and decline in hepatic blood flow (McLean and Le Couteur, 2004). Earlier findings have consistently demonstrated reduction in systemic clearance of drugs with high \(E_H\) in elderly individual. These drugs include propranolol, metoprolol, labetalol, verapamil, amitriptyline, imipramine, desipramine, doxepin, levodopa and pethidine (Butler and Begg, 2008). Similarly, the systemic clearance of drugs like warfarin, phenytoin, valproic acid, naproxen, ibuprofen, diazepam and lorazepam with low \(E_H\) depend on the activity of the drug metabolizing enzymes (George et al., 1995; Gardiner and Paine, 2011). Systemic clearance of drugs appears to be similarly reduced in parallel with reduced liver volume even in healthy ageing individuals (Bach et al., 1981).

Changes in the blood flow to the liver and the subsequent changes in drug metabolism induced by ageing process have potential to alter pre-systemic drug metabolism thereby modifying oral bioavailability (Wilkinson, 1997). This could be dangerous for drugs with narrow therapeutic index. Compared to younger adult where minor modification of drug metabolism by way of inhibition or induction may have no significant clinical consequence, the presence of age-related decline in metabolic activity in the elderly however, may make a little change in metabolic enzyme clinically deleterious. The expression and function of other phase I enzymes are also affected by the ageing process. A study has shown age-related decline in the metabolic activity of aspirin esterase (Summerbell et al., 1990; Yelland et al., 1991). Some other studies have reported frailty-associated reduction in the metabolism of a number of drugs including paracetamol (Wynne et al., 1990) and metoclopramide (Wynne et al., 1993). In addition, age-related changes in the general body mass, body composition and physiology of efflux proteins can also modify drug properties. Reduced total body mass and changes in the proportion of body water and fat can affect the drug-protein binding and volume of distribution of administered drugs (Bressler and Bahl, 2003; Kinirons and O’Mahony, 2003). Age-related changes in the gastrointestinal tract including reduced motility, secretion and blood flow may also influence the absorption profile of drugs.

In ageing individuals, there is a decrease in renal mass and blood flow with consequent decline in the renal functions including glomerular filtration and tubular secretion (Meyer, 1989). HIV-associated nephropathy may worsen the pharmacokinetic profiles of drugs that are principally excreted by the kidneys (Naftalin et al., 2011). Tenofovir and indinavir induce renal toxicity and may impair renal clearance of drugs and may be more dangerous when combined with other ARVs. This may be worse in ageing individuals who have lower creatinine clearance. NRTIs and PIs are hepatotoxic and may affect the metabolizing efficiency of the liver. Some expected drug interactions in the elderly have been considered so dangerous that such combinations have been contra-indicated. PIs are contra-indicated with cisapride due to the high risk of arrhythmias. Proton pump inhibitors reduce the gastrointestinal absorption of certain drug and are thus contra-indicated with delavirdine and atazanavir. Studies in man have also shown that ageing is associated with increased expression and function of P-gp in the human lymphocytes (Gupta, 1995). Compared to healthy population, renal disorders are more common in ageing HIV-infected individuals. This worsens renal contribution to DDI in this population.

**Comorbidity, multiple prescribers and drug use patterns**

Various studies have demonstrated the prevalence of various pathologic conditions in additions to AIDS-defining conditions in ageing HIV-infected individuals. These conditions include non-AIDS defining cancers, osteoporosis and other bone-related disorders (Pan et al., 2006; Anastos et al., 2007; Arnsten et al., 2007), hypogonadism (Crum-Cianflone et al., 2007), sexual dysfunction (Klein et al., 2005), dementia (Valcour et al., 2000). This age-related thymic atrophy (shrinkage from 70 g in infants to 3 g in the 70-year-old) is characterized by the replacement of thymopoietic with fatty tissue, leading to reduction in thymopoietic activities (Kuby et al., 2000). While HIV-1 infection is characterized by loss of naïve CD4\(^+\) T cells, dysfunctional CD4\(^+\) T cells increase with age (Bazdar et al., 2009). The influence of ageing on the immune system has thus, been shown to be responsible for faster disease progression in the elderly compared to HIV-infected young individuals (Effros, 2000). This faster progression and its associated comorbidity often necessitate earlier commencement of pharmacotherapy. DDI and its effects may be grossly exaggerated in ageing individuals due to frailty and ageing physiology. Ageing impairs both renal elimination and liver metabolism of drugs in most elderly patients. This may also apply to renal elimination due to declining renal function especially in individuals over 65 years old. These age-related changes are responsible for the known exaggerated effects of drugs in older people which are often seen as adverse drug reactions (Feely and Coakley, 1990).

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Depression, and other CNS disorders (Skaipik and Treisman, 2007). In a 10-year study to compare the rate of development of comorbidity in older (>50) and younger (25-35) Italian population, Orlando and co-workers (2006) found that 39 new cardiovascular, endocrine-metabolic and neurologic disorders were diagnosed in the older patients against four in the controls. In a study to assess the presence of comorbidity in HIV-infected individuals aged 55 years and older, 89% had one comorbidity or the other, with an average of 2.4 comorbidity per patient (Shah et al., 2002). In addition, treatment with ARVs has been shown to be associated with dyslipidemia and other metabolic disorders which may further compound drug management of comorbidity in ageing individuals (Vidal et al., 2011; Estrada and Portilla, 2011). This makes drug management of HIV in ageing patients complicated with the attendant co-medication. In another study to evaluate the relationship between the number of administered drugs and the potential for DDI, Johnell and Klarin (2007) assessed over 600,000 elderly patients from a Swedish drug register and reported 26% prevalence of type C potential DDI, 5% type D and a strong correlation between the number of drugs used and the risk of DDI.

The presence of various comorbidities makes ageing individuals with HIV/AIDS obtain health care from several health experts including infectious disease specialist and primary care professionals with an attendant poor integration of treatment plan. A study by Gebo et al. (2005) for examples showed that the rates of hospitalization among HIV-infected individuals aged 50 years and above increased between 1996 and 2000, while the rates for individuals between ages 18 and 30 decreased significantly. These factors of increased number of separate health experts involved in managing ageing patients, and the high hospitalization rates increase the risk of multiple prescription and DDI (Lieberman, 2000).

It has also been documented that CD4 cell recovery after the initiation of ART may be limited in older patients due to age-associated decline in immunity (Grabar et al., 2004; Silverberg et al., 2007). For example, studies have shown that ageing is associated with the involution of the thymus with resultant reduction in the thymic volumes which may limit CD4 recovery with treatment (Kalayjian et al., 2003). Thymic output has been shown to be minimal after age 55 years with significant decline in naïve T cells production and functionality (Effros, 2004; Naylor et al., 2005). The increased expression of T-cell chemokine co-receptors associated with ageing may reduce resistance to HIV infection in ageing individuals, thus facilitating the entry of the HIV virus into certain immune cells (Yung, 2003). Immunosenescence may result from the reduced production of IL-2 and IL-2 receptors, altering T cell function, and the progression of naïve to more terminally differentiated T-cells in the elderly (Simone and Appelbaum, 2008). These factors are believed to be responsible for the faster progression of HIV in older individuals. It has also been found that although older patients may achieve virologic suppression faster than younger patients; the achievement of immune recovery is less with advancing age (Saah et al., 1994). Further, these age-related changes because of their similarities to the AIDS-defining symptoms may be responsible for the higher rate of misdiagnosis of HIV/AIDS in the older population. They may also explain why older HIV-infected individuals are more prone to a cycle of opportunistic infections and other co-morbidities, polypharmacy and DDI (Kohler et al., 2000). Known DDI with ARVs are presented in Table 1.

### SPECIFIC COMPARATIVE STUDIES OF DDI IN AGEING HIV-INFECTED PATIENTS ON ART

The peculiar physiologic and pathologic conditions of HIV-infected ageing individuals have limited studies. A good understanding of the pharmacokinetic and pharmacodynamic properties of ARV and the physiology of ageing has made it possible to predict DDIs in the elderly. While most publications rely on these predictions, a number of case studies and studies have reported increased incidence of DDIs in this group of patients. Study types include risk assessment of DDI based on prescribed drugs using various DDI databases, case reports, and human studies. Kotb and co-workers reported a life-threatening case of DDI between ARVs and vinblastine. The 55-year old patient was prescribed a vinblastine monotherapy to manage multicentric Castleman's disease diagnosed while being treated with ARV combination of zidovudine, lamivudine, abacavir, nevirapine and ritonavir-boosted lopinavir (Kotb et al., 2006). This illustrates the increased predisposition to DDI as a result of age-related comorbidity and their management.

In a prospective cross sectional study carried out by Marzolini et al. (2011) to compare the potential for DDI in patients on ARV drugs and co-medications using age groupings according to ≤50 or ≥50 years, the study analyzed 1497 prescriptions of HIV-infected patients with 477 belonging to the upper age group. The documented drugs included ARVs, antibiotics and other co-medications for concurrent diseases, including self-prescribed drugs and herbal supplements. Using a drug interaction database for pharmacokinetic DDI screening, the authors reported 51% frequency of DDI in the upper age group compared to the 35% in the lower. The study found that older patients used certain drug classes more frequently than the younger ones. These include drugs in cardiovascular (53% against 19%); gastrointestinal (10% against 6%) and hormonal (6% against 3%) disorders. In this older population group, 27 and 22 DDIs occurred with cardiovascular and CNS drugs, respectively. The study attributed the higher incidence of DDI in the older
### Table 1. Clinically significant drug-drug interaction between ARV drugs and commonly used drugs in the elderly.

<table>
<thead>
<tr>
<th>ARV</th>
<th>Anti-infective agents</th>
<th>Cardiovascular drugs</th>
<th>Drugs used in CNS</th>
<th>Drugs in GIT disorders</th>
<th>Lipid modifying drugs</th>
<th>Others</th>
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<tr>
<td>Atazanavir</td>
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<td>Amiodarone</td>
<td>Omeprazole, ranitidine (Sekar et al., 2007); Lansoprazole (Tomilo et al., 2006)</td>
<td>Simvastatin (Schmidt et al., 2007)</td>
<td>Ethinyl estradiol, norethindrone (Sekar et al., 2008a)</td>
<td>Captopril (Guaraldi et al., 2006); Tacrolimus (Pea et al., 2008)</td>
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<td>Felodipine (Izzedine et al., 2004); Pravastatin (Aberg et al., 2006); Simvastatin (Hare et al., 2002)</td>
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group to the consumption of higher number of drugs due to co-medications (82% against 61%) with median number of 2 compared to 1 in the younger individuals.

In a French study to analyze the potential DDI between ARV and co-medications in elderly patients (median age 65.3 ± 5.2 years), 85% of the patients had a combination of three ARV while 94% of them had concomitant treatment with non-ARV drugs (4.6 ± 3.3 drugs per patient). The study found clinically relevant DDI in 45% of the prescriptions (Coroiu et al., 2010). Although the authors express that the result showed less frequent and less severe DDI than expected in this population, it is noteworthy that the difference is significant. In a retrospective study done in South Africa to determine the prevalence of DDI in different age groups of patients on ART, drug utilization review was performed on 47 085 ARV prescriptions. The authors identified 960 DDIs, 60.21% of which occurred in patients aged between 40 and 60 while patient group aged 60 and older had the lowest. This could be attributed to the fact that the study was limited to interactions between ARVs with no considerations for comorbidity. Further analysis showed that 1.88% DDI occurred in patients ≤6 years, 4.27% for patients 6 - 12 years, 0.63 for 12 - 19 years, 32.4% in patients 19 - 40 (Katende-Kyenda et al., 2008a). More DDS are reported to occur between ARVs and other drugs than with ARVs themselves. The same authors had reported that of 18035 DDIs found in ARV-containing prescriptions, 83.89% were DDIs between ARVs and other drugs compared to 16.11% between ARVs themselves (Katende-Kyenda et al., 2008b).

The conventional treatment with ARVs has been applied across adult age groups as no study has sufficiently indicated different treatment in ageing patients. The current guidelines do not take into cognizance the differences in the ageing physiology, the high propensity for comorbidity and the presence of disorders associated with ageing. Little research has been devoted to the ageing HIV-infected individuals. With the unfolding scenario of reduced new infections and the attendant high proportion of individuals ageing with HIV/AIDS, research in this area is necessary especially on the interactions between ARVs and co-medications in ageing individuals.

CONCLUSION

Drug therapy has been effective in the management of HIV/AIDS. This has led to an increasing proportion of HIV-infected individuals living and ageing with the disease. Due to several factors including polypharmacy and age-related co-morbidities, HIV-infected ageing individuals are at higher risk of clinically significant DDI. As shown by various studies, DDI in this group can compromise therapy. Health care providers must, therefore, bear in mind this risk, and be more selective in the choice of drugs in this population.

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