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Drug-Drug Interactions as a Challenge in the Treatment of HIV/AIDS

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1. Introduction

Human immunodeficiency virus (HIV) is a major challenge in the medical fraternity worldwide. According to the UNAIDS report on the global AIDS epidemic, in 2004 it had affected more than 42 million people, and of these 25 million resided in the sub-Saharan Africa (UNAIDS, 2004 & Bhigjee, 2005).

This virus has no cure; the lives of the infected patients can only be prolonged using lifelong highly active antiretroviral (ARV) therapy (HAART). HAART has been proven to suppress HIV-1 viral replication continuously thus reducing mortality and morbidity in treated patients. It has further been proven that HAART is only highly effective if prescribed in combination of more than 2 drugs. However these drug combinations can be presented with potential drug-drug interactions (DDIs) an important cause of adverse drug reactions (ADRs) (Highleyman, 2007).

DDIs are well-recognised causes of adverse drug effects (ADEs) (Bates *et al.*, 1995). According to Juurlink *et al.* (2003), DDIs do cause particularly important type of adverse drug event because they are often predictable based on previous reports, clinical studies, and an understanding of pharmacological principles.

According to Johnson *et al.* (1999), DDIs are classified as an important category of ADEs. Drug interactions result in undesirable modification of the action of one or more concurrently administered agents. The interaction may cause treatment failure, an increased pharmacologic effect, or a toxic effect, which may be fatal. Because DDIs usually have a specific time course (i.e., onset and duration), they are more predictable (and preventable) than ADRs (adverse drug reactions). Bates *et al.* (1999) state that Preventable DDIs account for about one third of ADEs but incur about one half of the total ADE costs.

In HIV-infected patients, the introduction of HAART has led to reduced morbidity and mortality in treated patients (Egger *et al.*, 2002). However, in a substantial proportion of patients, the effectiveness of HAART has not been sufficient due to occurrence of virological failure and immunological decay (Bartlett *et al.*, 2001). All this has been due to failure to determine drug interactions and prevention of toxic effects. (Boffito *et al.*, 2005).

The possible causes of DDIs include drug combinations, lack of communication between the prescribers and medical history, increase in the number of newly marketed drugs and polypharmacy. Specific patients who are risk for DDIs include the elderly, people living with HIV/AIDS. Patients with HIV are more at risk for the virus because they are treated

using HAART which consist of at least three agents with the risk rising from 13% in patients taking two drugs to 82% in those taking seven drugs or more (Sanderson, 2005).

The main focus in this abstract will be on the pharmacological aspects of DDIs between ARVs. The topics to be covered in this chapter will include:

1. The concept of DDIs.
2. The different types of DDIs.
3. Drug-drug interactions rating systems and their significance levels.
4. The possible causes of DDIs.
5. Patients that are at risk for DDIs.
6. The pharmacological aspects of DDIs between ARVs.
7. The role of pharmacists in preventing DDIs in clinical practice and;
8. Recommendations on the clinical management of DDIs.
9. Conclusion.

2. Concept of DDIs

The term drug-drug interactions can be defined as “*the pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone*” (Tatro, 2009). As described by Tatro (2009), the effect of a DDI may be one of the following:

- Antagonism, such as a loss of blood pressure control by clonidine when tricyclic antidepressants are added to a regimen.
- Synergism, as an example of which is the increased anticoagulant effect resulting from administering salicylates and warfarin.
- Idiosyncratic, such as the possible though rare severe effects that have been associated with patients concurrently receiving pethidine and monoamine oxidase inhibitor (Jankel & Fitterman, 1993).

3. Different types of DDIs

According to Seden *et al.* (2009), DDIs may arise due to the pharmacokinetics or pharmacodynamics of administered compounds. DDIs can be classified as pharmacokinetic or pharmacodynamics (Young, 2005; Cohen *et al.*, 2002) or pharmaceutical (Hall, 1986).

3.1 Pharmaceutical interactions

Pharmaceutical interactions occur when two drugs are given together, e.g., in an infusion, or when a drug reacts with the infusion solution. While it is necessary to be aware of this type of interaction, it is relatively uncommon (Hall, 1986).

3.2 Pharmacokinetic interactions

Pharmacokinetic interactions may be defined as those interactions in which the disposition of the first drug is altered by the second drug or precipitant drug. As a result, the effect of the first drug is either diminished or increased. Pharmacokinetic interactions are divided into those that affect (Swart & Harris, 2005; Young, 2005; Cohen *et al.*, 2002):

- **Drug absorption:** An example of this interaction is when didanosine containing an aluminium-magnesium antacid buffer, is administered with ciprofloxacin, the metallic

ions in the buffer may chelate with ciprofloxacin, resulting in subtherapeutic blood levels of ciprofloxacin (Sahai *et al.*, 1993).

- **Drug binding:** This was illustrated by in vivo work which showed that methadone concentrations were decreased when administered with ritonavir, due to displacement of methadone from plasma binding sites (Piscitelli & Gallicano, 2001).
- **Drug metabolism:** An example of this kind of interaction is between PIs and NNRTIs that act as inhibitors or inducers of cytochrome P450 (CYP450). Ritonavir is the most potent CYP450 and therefore the most likely to interact with other drugs such as amiodarone, cisapride or pethidine. Likewise efavirenz induces the metabolism of indinavir and saquinavir by reducing their plasma concentrations (Piscitelli & Gallicano, 2001).
- **Excretion:** In this case, the NRTIs may have additive or synergistic adverse effects, so if for example stavudine is administered with zalcitabine or didanosine, because these drugs are eliminated primarily by the kidney peripheral neuropathy caused by stavudine (Lee & Henderson, 2001).
- **Transport system:** One case report demonstrated a 48% decrease in valproic acid concentration after a patient had been started on lopinavir/ritonavir-based regimen. This interaction was likely to be due to the ability of ritonavir to induce valproic acid metabolism via glucuronidation (Sheehan *et al.*, 2006).

The result of pharmacokinetic DDIs may be an increase or decrease in the concentration of the drug at the site of action. The mechanism most common is drug metabolism.

3.2.1 Drug metabolism interactions

Drugs are metabolised by two types of reactions: phase 1 reactions that involve oxidation, reduction or hydrolysis in which drugs are turned into more polar compounds and phase II reactions that involve coupling drugs with some other substance (e.g. glucuronic acid) to make (usually) inactive compounds (Cohen *et al.*, 2002). These reactions make drugs more easily excretable. Drug metabolism interactions can increase or decrease the amount of drug available by inhibition or induction of metabolism (Cohen *et al.*, 2002).

3.2.1.1 Enzyme induction

Enzyme induction frequently affects phase 1 oxidation, which requires the presence of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and the haem-containing protein cytochrome P450. Enzyme inducers like carbamazepine, phenytoin, phenobarbital, PIs and NNRTIs, increase the activity of the microsomal enzymes (cytochrome P450 isoenzyme), increasing the rate of metabolism and excretion. One study reported that there was a decreased metabolism and subsequent toxicity of carbamazepine when concomitantly administered with ritonavir (Bates & Herman, 2006; Young, 2005). A case study reported of a patient who was prescribed ritonavir with midazolam concomitantly, and developed extreme sedation and possibly respiratory depression due to the inhibition of midazolam metabolism.

3.2.1.2 Enzyme inhibition

Enzyme inhibitors inhibit the microsomal enzymes (cytochrome P450 isoenzymes), decreasing the rate of metabolism and excretion of other drugs that are metabolised by these same enzymes (Cohen *et al.*, 2002). Examples of these drugs are PIs and delavirdine presenting drug interactions with statins because they are metabolised by the same enzyme (Geletko & ZuWallack, 2001). These drugs begin to accumulate in the body and toxicity may

develop within 2 to 3 days. The clinical significance of the enzyme inhibition interaction depends on the extent to which serum levels rise. Some drugs may have additive or synergistic adverse effects. For example, zidovudine may cause anaemia and neutropenia, so drugs causing bone marrow suppression should be prescribed with caution if used concomitantly (Matheny *et al.*, 2001). Another example of this metabolism was the administration of simvastatin with saquinavir/ritonavir, the interaction leading to increased levels of simvastatin by more than 3000% (Fichenbaum *et al.*, 2002b). This could put the patient at risk for adverse effects like myalgias, rhabdomyolysis, elevated creatinine phosphokinase and hepatic dysfunction (Dube *et al.*, 2003).

3.2.2 Cytochrome P450 isoenzymes

Cytochrome P450 is a large family of related isoenzymes of which about 30 have been identified. The most frequently involved in drug interactions are CYP3A4 and CYP2D6. There are many drugs that are metabolised by these cytochrome P450 isoenzymes including ARVs (Clarke *et al.*, 2008). Drugs may be metabolised by more than one cytochrome isoenzyme. For example, the majority of PIs and NNRTIs and antidepressants are substrates for, and can inhibit or induce the CYP450 system and have the potential to cause clinical drug interactions including serotonin syndrome, a potential fatal complication. According to Swart and Harris (2005) it is of value to know which particular isoenzymes are responsible for the metabolism of a specific drug as this makes it possible to predict with which other drugs it may possibly interact.

3.3 Pharmacodynamic interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action, without alterations in the concentrations of either drug (Young, 2005; Cohen *et al.*, 2002). Sometimes one drug competes directly with another for particular receptors, but often the reaction is more indirect and involves the interference with physiological mechanisms, making pharmacodynamic interactions more difficult to classify than pharmacokinetic interactions (DeVane as quoted by Delafuente, 2003). There are four basic subdivisions as quoted by Swart and Harris (2005):

- Additive or synergistic interactions and combined toxicity
- Antagonistic or opposing interactions
- Interactions due to changes in drug transport mechanisms
- Interactions due to disturbances in fluid and electrolyte

3.3.1 Mechanisms of drug-drug interactions

Drugs interact with one another through various mechanisms which include altered absorption, altered distribution, altered metabolism and altered elimination.

3.3.1.1 Altered absorption

Drug interactions can occur where one drug changes the absorption characteristics of another drug. The binding of one drug to another causes changes in gastric pH, and changes in gastrointestinal motility and can cause these drug interactions (Cohen *et al.*, 2002). One example is that of didanosine which contains an aluminium-magnesium antacid buffer. When administering didanosine with ciprofloxacin, the metallic ions in the buffer may chelate concomitantly with ciprofloxacin resulting in subtherapeutic levels of the antibiotic

(Sahai *et al.*, 1993). It is therefore recommended that the two drugs be administered at different times. Absorption of many drugs, such as delavirdine, atazanavir, aspirin, ciprofloxacin, and digoxin, can be significantly impaired by concurrent administration of antacids by a variety of mechanisms (Fulco *et al.*, 2006).

3.3.1.2 Gastrointestinal motility

A mechanism of DDIs that may go unrecognised is where one drug changes the gastrointestinal transit time. In doing so, the pharmacokinetics of not altering the transit time can be changed, leading to changes in the drug's pharmacological actions. Drugs with anticholinergic properties and opioids will slow gastrointestinal motility, while drugs, such as metoclopramide and laxatives will increase gastric emptying and gastric transit and generally increase the rate of absorption (Benet *et al.*, 1990).

3.3.1.3 Altered gastric pH

Drugs that change the normal pH of the stomach can affect absorption characteristics of other drugs. This is an essentially important point, considering the widespread use of proton pump inhibitors, although only a few clinically relevant interactions have been identified (e.g. ketoconazole) (Delafuente, 2003). The results of data in a study done by O'Connor-Semmes *et al.* (2001) suggested that the elderly may be more sensitive to the increase in gastric pH compared to younger adults.

According to Piscitell and Gallicano (2001), when didanosine is administered with indinavir, changes in pH may significantly alter drug absorption of indinavir because of an increase in pH due to the didanosine buffer. It is therefore recommended that didanosine and indinavir be administered at least one hour apart.

It has been reported by Fulco *et al.* (2006) and Tran *et al.* (2001) that acid-suppressive therapy with histamine-2 (H₂) blockers, proton pump inhibitors or antacids can cause a decrease in the absorption of some PIs. This is due to changes in the pH of the gastrointestinal tract. PIs like atazanavir, fosamprenavir, tipranavir have been found to have significant interactions with acid-suppressive therapy that require intervention due to the potential for virological failure from inadequate ARV concentration (Fulco *et al.*, 2006).

3.3.1.4 Altered distribution

The most common DDI affecting drug distribution is alteration in protein binding. This type of interaction occurs when there is competitive inhibition for protein binding sites. This allows for the unbound fraction of the drugs to be increased, and it is the free fraction that is responsible for pharmacological activity (Young, 2005). Most of the clinically significant interactions involve drugs that are highly protein bound and have a narrow therapeutic index. An example of this is when the cytidine analogue lamivudine inhibits phosphorylation of another cytidine analog, zalcitabine, resulting in high incidence of toxicities. Therefore such combinations should be avoided (Young, 2005).

An example of this DDI is when zidovudine and stavudine are co-administered, the two NRTIs do compete for cellular thymidine kinase, the enzyme that is responsible for the monophosphorylation of both drugs to nucleotides. The inhibitory effect impairs the efficacy of stavudine when combined with zidovudine (Havril *et al.*, 2000).

3.3.1.5 Altered metabolism

3.3.1.5.1 Cytochrome P450 isoenzyme

Most of the clinically important types of pharmacokinetic DDIs are those altering a drug's metabolism. Many elderly patients, but not all, have underlying impaired CYP450

metabolising capability. According to Flockhart and Tanus-Santos (2002), six CYP450 isoenzymes that have been identified to be involved in oxidative metabolism of most commonly used drugs are: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Interactions involving the CYP450 enzymes are often due to either inhibition of an isoenzyme, leading to increased blood or tissue concentrations of the substrate, or induction of an isoenzyme, causing enhanced metabolism and lower substrate concentrations (Delafuente, 2003:137). According to Johnson *et al.* (1999) enzyme inhibition is the mechanism most often responsible for life-threatening interactions.³² Such interactions have been observed when zalcitabine is combined with stavudine or didanosine producing severe peripheral neuropathy, pancreatitis, and lactic acidosis (Simpson & Tagliati, 1995).

Induction of certain CYP450 isoenzymes, for example CYP2C9/19 by lopinavir/ritonavir and nelfinavir was reported by Honda *et al.* (1999) that it could lead to an increase in the metabolism of antiepileptic drugs like phenytoin, a narrow therapeutic index drug. The reduction in the anticonvulsant serum concentration could lead to seizures.

3.3.1.5.2 Cytochrome P450 inhibition

Competitive binding at the enzyme's binding site between two drugs is often responsible for inhibition of a drug's metabolism. The onset of CYP450 inhibition depends on the inhibiting drug's half-life. For drugs with short half-lives, enzyme inhibition occurs quickly and clinically significant interactions can be apparent within 1 or 2 days (Cheng *et al.*, 2009). Inhibition of CYP450 is also dose-dependent. Higher doses of an inhibitory drug will cause greater amounts of competitive inhibition than lower doses. Although sufficient data are not available to help in clinical situations as stated by Delafuente (2003), knowing the CYP450 enzymes involved in a drug's metabolism can be used to predict and avoid clinical problems resulting from drug interactions.

All currently marketed PIs – atazanavir, amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir (Young, 2005) – and the NNRTI delavirdine inhibit CYP3A4 (Piscitelli & Gallicano, 2001) decrease the hepatic clearance of CYP3A4 substrates and increase their plasma levels.

3.3.1.5.3 Cytochrome P450 induction

The onset of enzyme induction is usually longer than that of enzyme inhibition (Chapron, 2001). Enzyme induction is dependent on the half-life of the synthesis of new CYP450 isoenzymes and is dependent on the half-life of the inducing drug. Like inhibition of CYP450 enzymes, shorter half-life drugs will have a shorter onset of induction. A drug with half-life, such as phenobarbital, may take one week before enzyme induction is seen.

Drugs often involved in induction of CYP450 isoenzymes are carbamazepine, phenytoin, phenobarbital, primidone, and rifampicin (Clarke *et al.*, 2008). Aging may impair enzyme induction, but this is not a universal finding as stated by Chapron (2001).

Of the ARVs, the NNRTIs nevirapine and efavirenz induce CYP3A4, thus increasing the hepatic clearance of CYP3A4 substrates and decreasing their plasma levels (Piscitelli & Gallicano, 2001). Other ARVs like PIs induce CYP450 isoenzymes, and it has been reported that drugs like phenytoin, rifampin, carbamazepine, phenobarbital, and dexamethasone can increase the hepatic clearance and therefore decrease plasma concentrations of the PIs (Lesho & Gey, 2003).

3.3.1.5.4 Altered renal elimination

Many drugs and drug metabolites are excreted in the urine via renal tubular secretion. Two drugs can compete for the same active secretion sites in the tubule allowing for decreased elimination and potentially toxic serum concentrations (Lesho & Gey, 2003). Alteration in urine pH can also affect drug elimination. Alkalinisation of the urine will decrease elimination of drugs that are weak bases and decreases in urine pH will increase their elimination. Acidification of the urine will decrease renal elimination of drugs that are weak acids (Hasten, 1995).

This mechanism happens in interactions that alter drug bioavailability by decreasing it and these are commonly found in PIs. The reason is that PIs induce CYP450 isoenzymes, so drugs like phenytoin, rifampin, carbamazepine, phenobarbitone, and dexamethasone can increase the hepatic clearance, thereby decreasing plasma concentrations of the PIs (Lesho & Gey, 2003). All this result in increase in toxicity of the drugs (Lesho & Gey, 2003). In the elderly as stated by Delafuente (2003), more common and potentially more significant are DDIs that affect renal function. Glomerular filtration rates decline with advanced aging. To compensate for this physiologic change, a compensatory production of vasodilatory renal prostaglandins occurs (Delafuente, 2001). However, according to Swedko *et al.* (2003) in frail elderly patients, serum creatinine concentrations may be very misleading, often in the normal range despite poor renal function.

4. DDIs rating system: significance levels

Most rating systems as employed by Tatro (2009) and De Maat *et al.* (2004) indicate:

- major significance,
- moderate significance; and
- minor significance.

4.1 Major significance: level 1

Significance level 1 indicates a major contradiction or a drug interaction that requires very careful monitoring. According to Strain *et al.* (2002b) the effects are potentially life-threatening or capable of causing permanent damage. The clinician needs to document why he or she is prescribing this combination, and the medical necessity to use both drugs concomitantly only if there is no alternative or the potential benefit outweighs the risk. Drug combinations producing an interaction with a significance level 1 are combinations that result in serious and potentially life-threatening adverse effects such as arrhythmia, respiratory depression and/or death (Winston & Boffito, 2005).

Obviously, if this combination is to be used the drug(s) in question must be prescribed with an explanation as to the need for their concomitant use and must be preceded by very cautious monitoring. Documentation of the clinician's awareness of the potential serious - level 1 - interaction should be accomplished at the time of prescribing this potentially dangerous combination. In addition, it is obligatory to alert the other health care providers' of the potential interactions and adverse outcomes which they could expect. Obviously, the optimum choice, if possible, is to use an alternative medication to avoid significance level 1 interactions (Strain *et al.*, 2002a).

4.2 Moderate significance: level 2

With significance level 2, the effects may cause deterioration in a patient's status. Additional treatment, hospitalisation or extension of hospital stay may be necessary (Strain *et al.*,

2002b). The potential interaction must also be documented and the clinical outcome(s) must be monitored carefully so that unacceptable, pernicious reactions are halted as soon as possible. According to Strain *et al.* (2002b) it is essential that the clinician document that the potential drug interactions were considered when using this combination. It is also essential to alert the patient's health care providers to the potential interactions so that they are observed early in their course.

4.3 Minor significance: level 3

As stated by Strain *et al.* (2002b) the effects are usually mild. Consequences may be bothersome or unnoticeable, but should not significantly affect the therapeutic outcome. Additional treatment is usually not required (Tatro, 2005 & Sewester, 2001). According to Strain *et al.* (2002a) significance level 3 does not preclude the use of a specific drug, but clinical decision making requires acknowledging if the adverse reactions (e.g. nausea and rash) might be precluded by choosing an alternative drug. The potential interaction and its mechanism(s) needs documentation in the patient's medical chart and the patient's health care providers need to be informed.

Another rating system is employed by *Drug Interaction Facts* which utilises 5 point significance classification scheme (Tatro, 2009) and *Facts and Comparisons* (McEvoy, 2000) and they recommended the following:

- Avoid combination: risk always outweighs benefit.
- Usually avoid combination: use combination only under special circumstances.
- Minimise risk: take action as necessary to reduce risk.
- No action needed: risk of adverse outcomes appears small.
- No interaction: evidence suggests no interaction.

5. Possible causes of DDIs

5.1 Drug combinations

Drug combinations of interacting drugs are among the major causes leading to DDIs (Seden *et al.*, 2009). Drug combinations are more common in an elderly population using many drugs (Björkman *et al.*, 2002). A large proportion of these combinations are likely to be part of a normal drug regimen. In a study done by Björkman *et al.* (2002), in DDIs most of the drug combinations increased the risk of ADRs and lowered therapeutic effects as stated by Seymour and Routledge (1998). In all potential DDIs, 50% of the combinations could result in an adverse drug reaction and 50% in a suboptimal therapeutic effect. However, combination ARV treatment is a potent and effective therapy for HIV infection (Pontali, 2008). This is also a disadvantage because ARV drugs frequently interact amongst themselves and other drugs as was identified by KatendeKyenda *et al.* (2007). Since some of these drug combinations have negative effects, more attention must be focused on detecting and monitoring patients using such combinations and could also be addressed by dose adjustment.

5.2 Lack of communication and medication history

Communication between emergency departments and primary care physicians often does not occur (Beers *et al.*, 1990), and primary care physicians do not take down medication histories optimally and therefore, the physicians responsible for follow-up may be unaware of the changes made in therapy.

Emergency department physicians do not routinely screen for potential drug interactions due to unavailability of a medication history. In a study by Beers *et al.* (1990) it was stated that groups of patients at higher risk of drug complications, the elderly and those taking multiple medications, did not appear to receive more cautious care. Neither the physician's record nor the instructions given to the patient indicated that prescribing physicians recognised the potential adverse reactions that were introduced. There is need for physicians to screen for interactions. A patient's advanced age or a long list of medications should cause the physicians to be more reticent in prescribing. Fewer medications should be given to the elderly and to high medication users.

5.3 Increase in number of newly marketed drugs

There is a considerable number of newly marketed drugs with a growing number of possible combinations. Complex disease states often require the concurrent use of these drug combination therapies so as to be highly effective (Bergk *et al.*, 2004). Nevertheless, as supported by Merlo *et al.* (2001) multiple drug use is also associated with the occurrence of DDIs. Therefore the majority of these interactions can be compensated by dose adjustment or prevented by a well-considered sequence of administration (Bergk *et al.*, 2004). The considerable number of newly marketed drugs with a number of possible combinations raises the need to support general practitioners with the pertinent information for careful approach to patients.

5.4 Polypharmacy

Polypharmacy, the use of two or more medications by one patient, has become prevalent especially in elderly patients (Gaeta *et al.*, 2002). Beers *et al.* (1990) in their study showed that those 65 years of age and older used an average of two to six prescribed medications and one to four non-prescribed medications per day. The frequency of polypharmacy in the elderly increases the incidence of adverse drug reactions and interactions, and it is the most significant contributing factor for DDIs. Patient's past medical history and medication has to be evaluated by the physicians. According to Seden *et al.* (2009), polypharmacy is largely unavoidable for patients receiving ARVs in both the developed and developing world and resource-poor setting, with life-long treatment and change of drug combinations along the way.

6. Patients at risk for DDIs

Patients that are at risk for DDIs are discussed in this section with specific reference to the elderly and the HIV/AIDS patients.

6.1 The elderly

The incidence of adverse drug reactions and interactions in the elderly has been reported to be two to three times the incidence in younger patients (Nolan & O'Malley, 1998). According to Sloan (1992), this increased risk for the elderly may be related to impaired organ reserve capacity, multiorgan dysfunction, and altered pharmacokinetics and pharmacodynamics.

6.2 People living with HIV/AIDS

The HIV infection is treated by using HAART, which involves a regimen of at least three agents to be effective (Seden *et al.*, 2009). In a study on DDIs in general medical patients,

Sanderson (2005) found that the risk of DDIs rose from 13% in patients taking two drugs to 82% in patients taking seven drugs or more.

7. Pharmacological aspects of DDIs between ARVs

DDIs are a serious complication of taking multiple medications and account for 3% to 5% of all hospital medication errors (Leape *et al.*, 1995). According to Clarke *et al.* (2008), the consequences of drug interactions vary ranging from drug toxicities to therapeutic failures, or loss of effectiveness and can significantly affect a patient's clinical outcome. Of particular concern are drug interactions in patients infected with HIV who are receiving HAART because it involves a regimen of a least three agents (Seden *et al.*, 2009).

HAART has revolutionised the management of HIV-1 infection and the ARV therapy has improved steadily in terms of efficacy, tolerability, and dosing convenience since the advent of HAART in 1995 (Chandwani & Shuter, 2008). HAART consists of four classes that are available for ARV therapy: (Nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs; non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); and a fusion inhibitor). The strongly recommended regimen based on the existing efficacy data, is either NNRTI-based or PI-based HAART (Yeni *et al.*, 2004).

7.1 Clinically significant drug interactions associated with Highly Active Antiretroviral Therapy

One of the most challenging issues faced by health care providers treating patients with HIV-1 infection is the complex problem of DDIs associated with HAART (Seden *et al.*, 2009; Clarke *et al.*, 2008; Pontali, 2007; Cohen *et al.*, 2002). The guidelines for the initial treatment of HIV infection recommend the use of at least three ARVs (Bartlett *et al.*, 2006a), each of which is associated with significant drug interactions (DHHS, 2003). Drug interactions associated with HIV medications can be classified into those that alter the pharmacokinetics and those that alter pharmacodynamics (Seden *et al.*, 2009).

Pharmacokinetic drug interactions result in a change in pharmacokinetic parameters, such as the area under the curve (AUC), which measures drug exposure, peak concentration (C_{max}), through concentration or half-life (Young, 2005; Cohen, 2002). Pharmacodynamic interactions result in alterations in the pharmacologic activity of the medication; not causing a change in the pharmacokinetic (Young, 2005; Cohen, 2002). The most common drug interactions in HIV medicine are pharmacokinetic interactions as a result of a change in the absorption, distribution and metabolism and the result of the concurrently administered medication (Piscitelli & Gallicano, 2001).

7.2 Influence of cytochrome P450 (CYP450) on DDIs in HIV

The cytochrome P450 enzyme system is responsible for the biotransformation of drugs from active to inactive metabolites that are readily excreted by the body. DDIs are more common in PIs and NNRTIs (Seden *et al.*, 2009; Winston & Boffito, 2005; Young, 2005; Cohen *et al.*, 2002). Of the numerous isoenzymes of CYP450 that have been identified, the ones responsible for elimination of drugs used in HAART are CYP3A, CYP1A2, and CYP2D2 (Clarke *et al.*, 2008).

7.3 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs & NtRTIs)

The NRTIs are valuable ARV agents in the treatment of HIV infection because they constitute the "backbone" of highly active ARV therapy regimens (Waters & Boffito, 2007).

Drug interactions associated with NRTIs and NtRTIs are few because these drugs are not metabolised by the CYP450 system (Clarke *et al.*, 2008). However, drug interactions may still occur within these drugs as was demonstrated by Katende-Kyenda *et al.* (2008a). One of the few pharmacodynamic interactions encountered in HIV medicine occurs, for example with co-administered zidovudine and stavudine, since both drugs are thymidine analogues and they can compete for the same phosphorylation site in the growing chain of HIV DNA, resulting in an antagonistic, pharmacodynamic interaction (Piscitelli & Gallicano, 2001). It is therefore recommended that these two drugs never to be combined.

The use of didanosine (ddl) is complicated by drug interactions (Cohen *et al.*, 2002). It is a buffered tablet form containing magnesium and calcium to improve systemic absorption. It, however, interacts with certain antibiotics like ciprofloxacin, tetracycline and therefore, to minimise the interaction, didanosine should be administered at least two hours after or six hours before the fluoroquinolone (Knupp & Barbhaiya, 1999). Concurrent use of didanosine-buffered tablets may also impair the absorption of the PI atazanavir, since atazanavir requires an acidic environment for absorption (Product Information Videx EC, 2003). To minimise the interaction, patients should take a didanosine-buffered tablet two hours after or one hour before taking atazanavir.

The most significant didanosine drug interaction reported occurs when didanosine is used concurrently with the NtRTI tenofovir. The didanosine AUC increases by 60% and therefore it is recommended that in patients receiving these two drugs concurrently and weighing > 60 kg, the didanosine dosage should be reduced from 400 mg to 250 mg once daily or from 250 mg to 200 mg in patients who weigh less than 60 kg (Young, 2005). For severely underweight patients, the dose should be further reduced to 125mg once daily (Faragon & Piliero, 2004). All patients receiving concurrent tenofovir and didanosine should be closely monitored for didanosine -related toxicities such as pancreatitis, hyperlactatemia, and lactic acidosis, regardless of didanosine dosage adjustments.

7.4 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drugs in this group are prone to drug interactions because they are extensively metabolised via CYP3A4 and can act as either inducers or inhibitors of CYP3A4. Nevirapine and efavirenz are inducers of CYP3A4, while delavirdine is an inhibitor of CYP3A4 (Pfister *et al.*, 2003). Therefore, when one of these drugs is combined with a drug that is also metabolised by CYP3A4, a drug interaction may occur (Clarke *et al.*, 2008).

Nevirapine presents with numerous drug interactions, being a CYP3A4 inducer, and drug interactions associated with it lead to an increase in metabolism and reduced concentration of the co-administered drug. For example, when nevirapine is concurrently given with methadone, withdrawal symptoms may occur as a result of reduced methadone levels (Pinzanni *et al.*, 2000). Efavirenz is a potent inducer of CYP3A4 *in vivo*. Like the PIs, EFV is extensively metabolised primarily by the CYP3A4 (Pfister *et al.*, 2003).

The induction properties of efavirenz can result in reduced concentrations of concurrently administered drugs that are metabolised by CYP3A4 and it is therefore contraindicated with midazolam, triazolam and ergotamine derivative since there is a potential for increased drug concentrations of these medications and associated toxicity (Product Information Sustiva, 2003). Efavirenz, as a potent inducer of CYP3A4 is suggested to have a potential interaction with lopinavir and ritonavir, both of which inhibit CYP3A4. This interaction was

assessed in a parallel group study in which PI-experienced, NNRTI-naive, HIV-infected patients received different doses of these agents (Young, 2005).

7.5 Non-Nucleoside Reverse Transcriptase and Protease Inhibitors Interactions

When predicting potential drug interactions, it is important to know which P450 isoenzyme is responsible for the metabolism of a drug. Drug interactions between NNRTIs and PIs are common as was observed in a study by Katende-Kyenda (2008b), as all currently available agents in these two classes are metabolised mainly by the 3A4 isoenzyme of the CYP450 system (Fichtenbaum & Gerber, 2002). NNRTIs and PIs also inhibit or induce CYP3A4, decreasing or increasing hepatic clearance and, thereby, increasing or decreasing plasma levels, respectively, of drugs metabolised by CYP3A4. Therefore, depending primarily on the potency of each NNRTI or PI as an inhibitor or inducer of CYP3A4 and on the substrate affected, each one has a different drug interaction profile.

All currently marketed PIs – atazanavir, amprenavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir – and the NNRTI delavirdine inhibit CYP3A4 (Piscitelli & Gallicano, 2001). According to Von Moltke *et al.* (1998), ritonavir is the most potent CYP3A4 inhibitor and, consequently, has the most drug interactions, while amprenavir, indinavir, lopinavir, and nelfinavir appear to inhibit CYP3A4 equally, and saquinavir with the lowest inhibitory effect.

7.6 Effect of Protease Inhibitors on Nucleoside Analogues

The nucleoside analogue reverse transcriptase inhibitor, tenofovir, does not appear to inhibit CYP3A4 isoenzyme significantly and, like most inhibitors, is excreted by the kidneys. Tenofovir, unlike other NRTIs, is associated with several drug interactions, particularly a bidirectional effect (i.e. agent can alter plasma levels of the other) with atazanavir, while atazanavir raises plasma levels of tenofovir (Holder, 2003).

Indinavir does not alter the pharmacokinetics of zidovudine, stavudine or lamivudine (Perry & Belfour, 1996:928). This is because the optimal absorption of indinavir requires a normal (acidic) gastric pH whereas an acid medium rapidly degrades didanosine, which is formulated with buffering agents to increase the pH. Therefore the administration of indinavir and didanosine should be separated by at least 1 hour to avoid an interaction mediated by altered drug absorption (Perry & Balfour, 1996).

7.7 Effect of Non-Nucleoside Reverse Transcriptase Inhibitors on Nucleoside Analogues

Nevirapine is a potent and selective non-competitive inhibitor of reverse transcriptase (De Maat *et al.*, 2003). It does not compete with template or nucleoside triphosphates, and therefore a significant interaction would not be expected. Nevirapine may reduce plasma zidovudine concentrations by 25% but does not influence plasma concentrations of didanosine or zalcitabine (Murphy & Montaner, 1996).

NRTIs, unlike NNRTIs and PIs, are not metabolised by the hepatic CYP3A4 enzyme system and – the exception of zidovudine and abacavir – undergo renal rather than biliary excretion. Zidovudine undergoes hepatic glucuronidation and abacavir is metabolised in the liver by alcohol dehydrogenase (Barry *et al.*, 1999). Therefore, there is little potential for interaction between NRTIs and NNRTIs or between NRTIs and PIs. In addition, the NRTI class as a whole has fewer drug interactions than the NNRTI and PI classes have.

7.8 Protease inhibitor interactions

The PIs are extensively metabolised by the cytochrome P450 (CYP) enzymes present in the liver and small intestine (Winston & Boffito, 2005). Therefore drug interactions involving PIs will occur largely as a result of enzyme induction or enzyme inhibition (Barry *et al.*, 1999). Some PIs can alter metabolism and thus the plasma concentration of other PIs, creating complex drug interactions when a second PI is added to HAART. According to Van Heeswijk *et al.* (2001), additionally, favourably positive DDIs can increase the exposure to PIs, allowing the use of lower doses at reduced dosing frequencies with fewer dietary restrictions.

Protease inhibitors have differing affinities for the CYP3A4 isoenzyme. The most potent inhibitor of CYP3A4 is ritonavir (Cooper *et al.*, 2003), whereas the least potent is saquinavir. CYP3A4 inhibition associated with indinavir, nelfinavir, and amprenavir, and atazanavir tends to be intermediate. Ritonavir is often the most likely medication in the PI class to cause drug interactions because in addition to its CYP3A4 inhibition, it also inhibits CYP2D6 and induces CYP1A2 and CYP2C9 (Clarke *et al.*, 2009). However, ritonavir is often used to enhance the pharmacokinetic parameters of co-administered PIs like indinavir (Kappelhoff *et al.*, 2005), due to its potent inhibition of their metabolism by CYP3A4 (Zeldin & Petruschke, 2004).

The use of boosted double PI regimen is presented with complex unexpected pharmacokinetic interactions (Winston & Boffito, 2005). Therefore combinations like tipranavir/ritonavir with others must be avoided because such combinations have shown to significantly reduce plasma concentrations of saquinavir, amprenavir and lopinavir (Boffito *et al.*, 2005). Another interesting interaction that was observed by Boffito *et al.* (2005) was with the boosted double combinations of atazanavir/saquinavir/ritonavir. Saquinavir levels are enhanced in this regimen further than when dosed with ritonavir alone, thus suggesting a role for this as a once daily regimen.

8. Role of pharmacists in preventing DDIs in clinical practice

Although the number of clinically relevant DDIs is probably low, DDIs may be responsible for a substantial number of hospital admissions. Therefore the pharmacist is responsible for preventing the use of unsafe or non-effective drug regimens. Specifically, pharmacists should avoid the dispensing of combinations of drugs that may cause serious DDIs (Becker *et al.*, 2005).

Many drug interactions can be avoided or managed safely if adequate time and precautions are taken by a patient's pharmacist. Having the pharmacist provide patient counselling on the use of prescription and non-prescription medication, disease state(s), and the safety of concurrent use of herbal products plays a major role in avoiding drug interactions (Brown, 2004).

According to Lien and Lien (1994), many patients visit more than one doctor for their different diseases and receive more than one drug at a time, and often doctors are unaware of all the medications their patients are taking and the risks to which their patients are exposed when treated with multiple drugs. Since pharmacists in the community setting or hospital, are the most accessible health care providers, they are able to intervene when faced with potential drug interactions that may occur during patients' multiple drug therapy.

Adverse DDIs are the major cause of morbidity and mortality. Cancer patients, for example, are particularly at high risk of such interactions because they commonly receive multiple

medications, including cytotoxic chemotherapy, hormonal agents and supportive care drugs (Blower *et al.*, 2005). Increased awareness by pharmacists of the potential for drug interactions will allow health care providers to minimise the risk by selecting appropriate drugs and also by monitoring for signs of interaction.

According to Pezella (2005), in 2000, the number of patient deaths attributable to ADRs in the United States of America, was estimated to be 218 000 annually. More than 51% of approved drugs in the market in 2009 may have serious side-effects not detected before marketing approval. Therefore health plans and pharmacy benefit managers must work together to take effective steps to increase ADR monitoring and reporting and to proactively avoid ADRs through pharmacy management tools.

9. Recommendations regarding management of level 2 ARV DDIs in clinical practice

The overall review revealed that most DDIs are identified between ARVs interacting at level 2 as identified by Tatro guidelines. Therefore the following recommendations can be formulated to manage these DDIs, based on the standard treatment guidelines for ARVs.

- Patients must be told the importance of consulting their doctors before using over-the-counter drugs that might interact with their prescribed ARVs;
- The prescriber should always check for potential DDIs then prescribing any concomitant drug for a patient who is on ARV therapy;
- Drug level monitoring of concurrent patients' medications should be done;
- While DDIs involving HIV drugs are essentially unavoidable, many can be managed through dosage adjustments as recommended by McNicholl & Coffey, (2007 & 2009) and McNicholl, (2009).

10. Conclusion

This chapter dealt with drug-drug interactions as a challenge presented to healthcare providers in the management of HIV/AIDS. This worldwide epidemic can be managed using HAART which according to the recommended treatment guidelines, three or more drugs have to be prescribed. However some these combinations present with DDIs, the major cause of adverse drug events. DDIs can nevertheless be managed accordingly either by switching the drug combinations or by dosage adjustments. It is therefore the role both prescribers and specifically the pharmacists to identify the DDIs and working in collaboration manage them.

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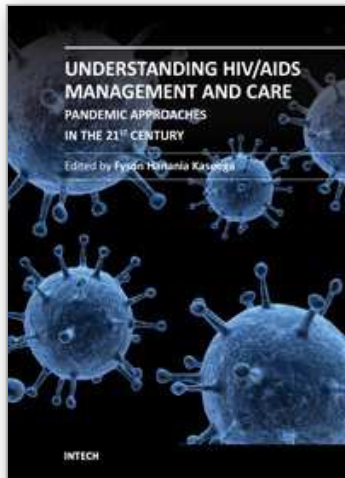
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Like any other book on the subject of HIV/AIDS, this book is not a substitute or exhausting the subject in question. It aims at complementing what is already in circulation and adds value to clarification of certain concepts to create more room for reasoning and being part of the solution to this global pandemic. It is further expected to complement a wide range of studies done on this subject, and provide a platform for the more updated information on this subject. It is the hope of the authors that the book will provide the readers with more knowledge and skills to do more to reduce HIV transmission and improve the quality of life of those that are infected or affected by HIV/AIDS.

How to reference

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