Drug Interactions During Periodontal Therapy in HIV-Infected Subjects

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Abstract: Despite the beneficial effect of the HAART, adverse reactions and drug interaction have been observed. Abnormalities in lipid and glucose metabolism make HIV-positive patients to high risk for the development of coronary heart disease and diabetes, respectively. Besides adverse reactions, drug interaction with other medication can also be observed. In fact, drug interaction may interfere in the periodontal therapy in HIV-infected individuals. For instance, fluconazole, ketoconazole, itraconazole, metronidazole, ciprofloxacin, midazolam and triazolam can interact with some antiretroviral medications, such as zidovudine, nevirapine and ritonavir. The aim of the current study was to show to periodontists and general dental practitioners the importance of understanding the drug interaction in HIV-infection in order to establish a better control during periodontal treatment.

Keywords: HAART, periodontitis, HIV.

INTRODUCTION

Therapeutic interventions in HIV infection have been up to now mainly directed towards two viral enzymes, reverse transcriptase and protease. This therapy has markedly changed the pattern of infection by the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). This antiretroviral therapy, which is known as highly active antiretroviral therapy (HAART), is capable of reducing viral load to undetectable levels and consequently to increase lymphocyte TCD4+ counts and as well as a substantial reduction of HIV-associated morbidity and mortality [1]. In addition, it has been shown that the introduction of the HAART for the medical management of HIV-infected patients has resulted in a marked decrease in the incidence and/or severity of periodontal disease [2-4].

Despite the beneficial effect of the HAART, the occurrences of adverse reactions and drug interaction have also been observed [5]. Adverse drug reactions are one of the important factors associated with reduced quality of life among HIV-infected patients taking HAART [6]. Abnormalities in lipid metabolism make HIV-positive patients to high risk for the development of coronary heart disease [7]. The mechanisms responsible for metabolic changes of anti-HIV drugs are not fully understood. Increase in serum triglycerides, low-density lipoproteins (LDL), and total cholesterol have been reported as well as the development of insulin resistance and lypodistrophy, which is characterized by peripheral subcutaneous lypoatrophy and relative central fat accumulation [8]. Zidovudine and stavudine, for instance, are the drugs mostly associated with lypoatrophy [9]. Several antiretrovirals such as amprenavir, indinavir, and saquinavir (protease inhibitors - PIs), zidovudine (nucleoside reverse transcriptase inhibitor - NRTIs) and stavudine (non-nucleoside reverse transcriptase inhibitors - NNRTIs), increase total cholesterol, LDL-cholesterol, and triglyceride concentrations [10]. Mechanisms of hepatotoxicity include direct antiretroviral toxicity, hypersensitivity, immune reconstitution in those with chronic viral hepatitis, and steato hepatitis secondary to mitochondrial toxicity caused by NRTIs. In addition, tenofovir can induce nephrotoxicity [11], and abacavir causes a hypersensitivity reaction, including fever, rash, fatigue, and gastrointestinal symptoms.

Besides adverse reactions caused by antiretroviral in HIV-infected patients, drug interaction with other medications can also be observed. During periodontal therapy, these interactions can occur when antiretrovirals are administered simultaneously with others drugs for the treatment of periodontal diseases [12]. In fact, drug interaction may complicate the success of the treatment in HIV-infected individuals and interfere with periodontal therapy. The aim of the current study was to show to periodontists and general dental practitioners the importance of understanding the drug interaction in HIV-infection in order to establish a better control during periodontal treatment.

DRUG INTERACTION MECHANISMS

Drug interactions may be categorized as pharmacodynamic (additive, antagonistic or synergistic effects at the

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level of mechanism of action in the target site) and pharmacokinetic (modulation of the time course and magnitude of drug concentrations in body compartments). Pharmacokinetic interactions can result from a variety of mechanisms, including the modulation of hepatic drug biotransformation, renal clearance, drug transportation, distribution and plasma protein binding [13].

Drug Biotransformation

An important mechanism of biotransformation is performed by cytochrome P450 (CYP) Isoforms. CYPs constitute a superfamily of haemoproteins that are expressed throughout the phylogenetic spectrum and catalyze the biotransformation of several endogenous substrates and xenobiotics. Although expressed in several tissues, the human drug-metabolizing CYPs are concentrated in the smooth endoplasmic reticulum of the liver, with lower levels of expression in the lungs, kidneys, intestine and brain. The multiple CYP enzymes are classified into families, subfamilies and isoforms based on a systematic nomenclature. The first number designates the 'family' (>40% sequence identity within family members), the letter that follows designates the 'subfamily' (>59% sequence identity), which is followed by a number indicating a particular CYP isoform. The major human drug-metabolizing CYPs belong to families 1, 2, and 3, the specific isoforms being 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3 A4, 3A5 and 3A7 [13]. Human cytochrome P450 (CYP) 3A4 is the most abundant hepatic and intestinal phase I enzyme that metabolizes approximately 50% marketed drugs. The ability of drugs to act as inducers, inhibitors, or substrata for CYP3A is predictive of their concurrent administration with a known CYP3A substratum which might lead to altered drug disposition, efficacy or toxicity [14].

While the liver is the principal organ involved in these processes, most tissues in the body, including the small intestine, kidney, neuronal tissue, and bloodstream, can participate depending on the drug or endogenous compound. Orally administered drugs that possess a high first-pass effect (i.e. a large percentage of the drug is chemically altered before entering the blood-stream), pre-hepatic biotransformation in the small intestine is now known to be an important site for metabolic drug interactions [15].

Highly Active Antiretroviral Therapy (HAART)

The antiretroviral drugs are classified in three groups: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) (Table **1**). Zidovudine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, tenofovir, adefovir, entricitabine, entecavir and telbivudine are antiretroviral drugs that belong to NRTIs group. Nevirapine, delavirdine, efavirenz, and etravirine are non-nucleoside reverse transcriptase inhibitors (NNRTIs). The PIs antiretroviral drugs are amprenavir, saquinavir, lopinavir, ritonavir, indinavir, nelfinavir, atazanavir, darunavir, fosamprenavir and tipranavi r[5]. In addition, a new class of antiretroviral, fusion inhibitors, has been described and its unique representative is the enfurvirtide (T-20) [15]. Currently, no significant interaction has been identified for this medication [5]. The advent of highly active antiretroviral therapy (HAART: combination of one or two NRTIs plus one NNRTI or IP), with the introduction of protease inhibitors in 1998, has been proved to be effective in suppressing HIV replication, increasing the number of CD4 lymphocytes, decreasing morbidity and mortality associated with the virus, and improving quality of life in adults as well as in infected children [16]. However, it has been associated with metabolic complication, such as hyperlipidaemia, diabetes mellitus, hypertension, lypodistrophy and osteopenia. Many of these drugs for the treatment of HIV infection can affect drug enzymes metabolism, potentially enhancing the effect and toxicity of concomitant drugs, or induce the metabolism of concomitant drugs with the reduction of efficacy. All currently available PIs are substrates of the hepatic CYP450 system (CYP). Of all the CYPs involved in drug metabolism,

Table 1. Categories of Antiretroviral Drugs

NRTIs	NNRTIs	PIs	Fusion Inhibitors
Zidovudine	Nevirapine	Amprenavir	enfurvirtide (T-20)
Zalcitabine	Delavirdine	Saquinavir	
Didanosine	Efavirenz	Lopinavir	
Stavudine	Etravirine	Ritonavir	
Lamivudine		Indinavir	
Abacavir		Nelfinavir	
Tenofovir		Atazanavir	
Adefovir		Darunavir	
Entricitabine		Fosamprenavir	
Entecavir		Tipranavir	
Telbivudine			

NRTIs = nucleoside/nucleotide reverse transcriptase inhibitors.
NNRTIs = non-nucleoside reverse transcriptase inhibitors.
PIs = protease inhibitors.

CYP3A4 is the most prominent. In addition, all PIs inhibit CYP3A4 to a varying degree. Ritonavir is by far the most potent inhibitor for CYP isoform, followed by indinavir, nelfinavir, amprenavir and saquinavir in decreasing order of potency [5, 15]. Both ritonavir and nelfinavir induce other cytochrome P450 isoforms (CYP2C9, 2C19, 1A2 and 2E1) as well as conjugative enzymes, UDP-glucuronosyltransferases, for which they have very low affinity. Thus, ritonavir and nelfinavir have the ability to induce drugs metabolism that are metabolized by these enzymes. Efavirenz is metabolized primarily by hepatic CYP3B6 with some involvement of CYP3A [5, 17].

DRUG INTERACTION DURING PERIODONTAL CLINICAL MEASUREMENTS

When HIV-infected patients seek for a periodontal treatment, it is important to consider the risk for and the management of potential drug–drug interactions. Initially, it may be necessary antibiotic prophylaxis and/or pain control pretreatment. After that, drug–drug interactions can occur during the treatment of the patient in the office setting. Finally, these interactions may also be observed when the patient is at home taking the medications prescribed for the postoperative management. As a matter of fact, there are several prescribed drugs for periodontal treatment that present potential interaction with antiretroviral (Table **2**).

Prior to periodontal clinical measurements, including probing depth (PD) and clinical attachment level (CAL), as well as the presence or absence of bleeding on probing and supragingival biofilm (plaque index), an oral examination of soft tissues can detect some oral lesions, such as infection caused by *Candida sp*. In this case, it is mandatory to control the opportunistic infection prior the periodontal treatment. Sometimes, it is necessary systemic antifungal therapy, mainly in severe immunodeficiency condition, when esophageal and oropharyngeal candidiasis dissemination is present. The azole antifungal agents, such as fluconazole and kenoconazole, are indicated for the treatment of these conditions. Nevertheless, fluconazole may increase the levels and effects of zidovudine. Zidovudine is eliminated primarily by glucuronidation, catalyzed by the enzyme UDP glucuronosyltransferase (UGT), and in humans generates 3'-amino-3'-deoxythymidine (AMT) and 5'-O-glucuronide (GAMT) [18, 19]. The glucuronidation acts in the elimination mechanism of a myriad of structurally different endogenous compounds and xenobiotics, including many prescribed drugs. Fluconazole, as well as amphotericin B, ketoconazole and miconazole are competitive inhibitors of zidovudine glucuronidation. For instance, coadministration of zidovudine and fluconazole produce a 43% reduction in the steady-state oral clearance of zidovudine, a 2.3-fold prolongation of zidovudine $t_{1/2}$ and a 48% decreased clearance of zidovudine glucuronide [20]. Like that, fluconazole may increase the myelosuppressive effects of zidovudine and, therefore, attention must be considered in case of coadministration of these two medications.

All the azole antifungal agent drugs are inhibitors of CYP enzymes. However, their potencies are vastly different and are also different for the various isoforms [13]. Two drugs from the azole group, ketoconazole and itraconazole, inhibit both cytochrome P450 isoenzymes 3A4 and P-glycoprotein [13, 21]. Many protease inhibitors, such as ritonavir, indinavir, nelfinavir and saquinavir, are metabolized by these two enzymatic systems, hence those antifungal must be administrated with attention in HIV-infection undergoing HAART [13]. In addition, fluconazole and ketoconazole increased levels of NNRTIs, such as nevirapine and etravirine, while itraconazole increased levels of etravirine [22]. Drugs in which absorption depends on the level of stomach acidity such as ketoconazole and itraconazole should be administered at least 2 hours prior to the buffered formulations of didanosine [5]. Darunavir is prescribed in combination with ritonavir and other antiretroviral agents. When administrated with ketoconazole, darunavir may present increased serum levels, while darunavir and ritonavir may increase the levels of ketoconazole.

DRUG INTERACTION DURING THERAPEUTIC PROCEDURES

Non-Surgically Periodontal Therapy

Periodontal therapy involves supragingival and subgingival mechanical debridement and establishment of a local environment for compatible bacteria with periodontal health [23]. In fact, the success of the treatment involves nonsurgically, surgically therapy, and long-term maintenance [24]. Meantime, antibiotics are commonly administrated before periodontal therapy because of the risk of endocarditis [25], infection in recent orthopedic joint replacement [26] and organ transplantation. In HIV-infected subjects with early asymptomatic HIV infection as well as in those with more advanced HIV-related immunodeficiency, neutropenia has been reported [27]. When neutrophil counts <1.000 cells/mm3 is observed, it may obligate antibiotics prophylaxis. Amoxicillin is a standard general prophylaxis, followed by clindamycin, cephalexin or cefadroxil, and azithromycin or clarithromycin. Among these medications, only clarithromycin, a macrolide antibiotics, has demonstrated drug interaction with antiretroviral because of its potent irreversible enzyme inhibitors of the cytochrome p-450 enzyme 3A4 (CYP3A4) [14, 18].

Periodontitis is caused by periodontal pathogens harbored in the dental biofilm. These bacterial species within complex bacterial communities may have important implications in the antimicrobial therapies aimed the fight against them. Like that, conventional therapies should be adapted to the present knowledge on biofilms [28]. Although there are not sufficient data to suggest that antibiotics might help in the treatment of periodontitis considering that the optimum protocol has not yet been clearly defined [24], the adjunctive benefits of using systemic antimicrobials in the treatment of periodontitis have already been reported [24, 28, 29]. It is clear that systemic antimicrobials may have a role in the treatment of periodontitis, but their prescription should be particularly restricted to medically compromised patients, such as diabetes mellitus, and specific periodontal conditions [28-30], like necrotizing periodontal disease, aggressive periodontitis and advanced chronic periodontitis.

Systemic antibiotics have been administrated after debridement and a variety of antibiotic have been recom-

Table 2. List of Drugs Prescribed During Periodontal Therapy that Interacts with Antiretroviral [5, 13, 14, 20-22, 33]

Categories of Drugs	Antiretroviral	Consequence of interaction
Antifungals		
1.Fluconazole, Amphotericin B, Miconazole	Zidovudine	Increase levels and effects of zidovudine.
2.Fluconazole	Nevirapine	Increase nevirapine levels. Possible increase in hepatotoxicity with coadministration requiring monitoring of nevirapine toxicity.
3. Ketoconazole	Zidovudine	Increase levels and effects of zidovudine.
	Nevirapine	Increase ketoconazole levels by 63%. Increase nevirapine levels by 15−30%. Do not recommend coadministration with nevirapine.
	Etravirine	Increase levels of etravirine. Decrease ketoconazole levels.
	Indinavir,	Increase levels and effects of indinavir.
	Saquinavir	Increase saquinavir levels threefold.
	Lopinavir	Increase lopinavir levels. Increase ketoconazole levels threefold.
	Ritonavir	Increase levels and effects of ritonavir.
	Didanosine buffered	Decrease of absorption of ketoconazole.
	Darunavir	Increase of serum levels of darunavir.
4. Itraconazole	Ritonavir, indinavir, nelfinavir, saquinavir	Increase of levels and effects of antiretroviral.
	Etravirine	Increase levels of etravirine. Decrease itraconazole levels.
	Didanosine buffered	Decrease of absorption of itraconazole.
	Lopinavir	Increase itraconazole levels.
Antibiotics		
5. Erythromycin	Indinavir, atazanavir	Increase of levels and effects of indinavir and atazanavir.
	Nevirapine	Decrease of levels and effects of erythromycin.
6. Azithromycin	Nelfinavir	Increase of effects of nelfinavir
7. Metronidazole	Ritonavir	oral solution Disulfiram-like reaction
	Zalcitabine, stavudine	Increase of risk of peripheral neuropathy.
	Nelfinavir, fosamprenavir	Risk of propylene glycol toxicity.
	All currently available PIs	Increase of adverse effects or toxicity of PIs.
8. Tetracycline	Didanosine buffered	Decrease of absorption of tetracycline.
9. Doxycycline	Didanosine buffered,	Decrease of absorption of doxycycline.
	Indinavir and atazanavir	Increase of levels and effects of indinavir and atazanavir.
10. Minocycline	Didanosine buffered	Decrease of absorption of minocycline.
11. Ciprofloxacin	Didanosine buffered	Decrease of absorption of ciprofloxacin
	All currently available PIs	Increase of adverse effects or toxicity of PIs.

(Table 2). Contd…..

Local anesthetic		
Categories of Drugs	**Antiretroviral**	**Consequence of interaction**
12. Lidocaine	Delavirdine, ritonavir, indinavir, atazanavir, fosamprenavir and tipranavir	Increase of levels and effects of lidocaine (systemic).
Analgesic		
13. Tramadol, Meperidine, Propoxyphene	Ritonavir	Increase of levels of analgesic.
Benzodiazepines		
14. Diazepam	Delavirdine, efavirenz	Increase of levels and effects of diazepam.
15. Alprazolam	Delavirdine, efavirenz, indinavir	Increase of levels and effects of alprazolam.
16. Midazolam, Triazolam	Saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, darunavir/ritonavir, fosamprenavir and atazanavir	Increase of levels and effects of benzodiazepines (midazolam and triazolam)

mended including amoxicillin, amoxicillin and clavulanate, metronidazole, tetracycline, ciprofloxacin and doxycycline, azithromycin, spiramycin, clindamycin, amoxicillin and metronidazole, ciprofloxacin and metronidazole [28, 31, 32]. Among them, only metronidazole and ciprofloxacin are inhibitors of CYP3A4: the first presents a weak inhibition and the second is a reversible inhibitor [33]. Inhibition of these enzymes has resulted in several fold increases in the concentration of concurrently administered medications, like antiretrovirals which are also metabolized by the same enzymes. In addition, interaction drug's metabolism results in increased and prolonged antiretroviral concentrations, which could result in greater adverse effects or toxicity [10].

Other interaction has been observed with didanosine buffered tablets and pediatric oral solution and may decrease absorption of quinolones or tetracyclines. Therefore, it has been suggested administration 2 hours prior to didanosine buffered formulation [5]. Of interest, it is recommended to avoid all ethanol or any ethanol – containing drugs, because they may cause disulfiram-like reaction characterized by flushing, headache, nausea, vomit, sweating or tachycardia [5]. As ritonavir oral solution contains 45% ethanol, concurrent use with metronidazole is contraindicated. Metronidazole is also associated with peripheral neuropathy and may increase the risk of peripheral neuropathy of zalcitabine and stavudine. In addition, concurrent use of oral solution of nelfinavir or fosamprenavir (Telzir®) with metronidazole is contraindicated, due to the risk of propylene glycol toxicity [5]. Metronidazole is generally prescribed for anaerobic oral infections treatment and penicillin for aerobic infection treatment. Considering that metronidazole presents several interactions with antiretroviral, clindamycin may be the medication of choice for both anaerobic and aerobic infections, such as periodontitis [12]. Nevertheless, high rates of hypersensitivity reactions to clindamycin have been noted in HIV infected patients [34].

The macrolide antibiotic azithromycin does not inhibit hepatic enzymes and is a safe alternative drug for patients under antiretroviral therapy. However, the azithromycin may increase the effects of nelfinavir. The erythromycin, also a macrolide, is rarely administrated in periodontal treatment, but the knowledge of some interactions with antiretrovirals may be important. Nevirapine, for instance, may decrease the levels and effects of erythromycin. Furthermore, the levels and effects of indinavir and atazanavir may be increased by erythromycin [5].

Doxycycline rarely has been prescribed for periodontal infection. Nowadays, this medication has been recommended mainly in sub antimicrobial dose, which has become widely established as an effective adjunctive systemic therapy in the management of periodontitis [35]. However, the levels and effects of indinavir and atazanavir may be increased by doxycycline [5].

Local anesthetic is necessary for scaling and root planning during periodontal debridement. Local anesthetics frequently contain vasoconstrictors and their presence provides the greater source for potential drug–drug interactions than the local anesthetic itself does [12]. Nevertheless, interactions between vasoconstrictors and antiretroviral therapy have not yet been observed. Regarding to the local anesthetic, it has been observed interaction with lidocaine. Delavirdine, ritonavir, indinavir, atazanavir, fosamprenavir and tipranavir may increase the systemic levels and effects of

lidocaine, which must be monitored its serum concentrations. In addition, the increase of serum concentrations of lidocaine may potentially lead to toxicity [5].

Surgery Periodontal Therapy

In certain situations, periodontal surgery may be necessary with the purpose of correction of sequel by the destructive periodontal disease, such as alveolar bone defects and furcation involvement. In this case, it may be necessary a systemic antibiotic in association with periodontal surgery or regenerative surgery. For these procedures, several antibiotics have been recommended, such as phenoxymethyl penicillin, tetracycline, amoxicillin/clavulanate, ofloxacin, ciprofloxacin, doxycycline, metronidazole, minocycline, ornidazole [28]. According to previously mentioned medications only metronidazole, ciprofloxacin, tetracycline, azithromycin have shown interaction with antiretroviral therapy. Thus, before prescribe some antibiotics for HIV infected individuals, it is recommended to contact the patients' physician.

Pain is usually a common complaint followed periodontal surgery and, therefore, analgesic and anti-inflammatory prescriptions are sometimes necessary. Acetaminophen is one of the most commonly self-administered and prescribed medications [12], but it has not been observed interaction with antiretroviral. However, serum concentrations of the patient drug and/or metabolites of others analgesics (e.g., tramadol, meperidine, propoxyphene) may be increased by the use of ritonavir. In addition, in many situations, in order to relax the patients, the administration of behavior-modifying agents before the surgical procedure may be indicated. Benzodiazepines are frequently utilized to achieve this aim. These drugs are metabolized by the cytochrome P450 enzymes, primarily 3A4, and therefore susceptible to pharmacokinetic drug interactions [33]. Similarly, agents that induce this enzyme will reduce the effectiveness of the benzodiazepines and on the other hand agents that inhibit it will increase its effects, possibly leading to toxicity [12]. In HIV infected patients, several interaction between benzodiazepines and antiretroviral have been observed. Delavirdine and efavirenz (NNRTIs), for instance, may increase the levels and effects of some benzodiazepines, such as diazepam and alprazolam. Saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, darunavir/ritonavir, fosamprenavir and atazanavir (PIs) may increase the levels and effects of selected benzodiazepines and therefore are contraindicated with midazolam and triazolam, while indinavir is also contraindicated with alprazolam [5].

Final Comment

In 2007, there were 2.7 million new HIV infected people and 2 million HIV-related deaths. Sub-Saharan Africa remains the most heavily population affected by HIV, accounting for 67% of all living people with HIV and for 75% of AIDS deaths in 2007 [36]. However, AIDS epidemic is still present in several places of the world. In many countries, such as China, Indonesia, Kenya, Mozambique, Papua New Guinea, Russian Federation, Ukraine and Vietnam, the rate of new infected people have increased. In countries such as Germany, United Kingdom and Australia the growth of new cases has also been observed. Currently there are 33 millions of individuals living with the HIV all over the world [36], and it is almost impossible that dental practitioners all over the world have not seen at least one HIV-infected patient for treatment. In fact, management of the periodontal diseases in HIV-infected patients is a fundamental part of the periodontists. Furthermore, it is very important to have an updated knowledge about HIV-infections, as well as to understand the possible drug interaction between HAART and periodontal therapy. More important than the success or failure of periodontal care, it is a complete understanding of the mechanisms involved and the risk of drug interaction in these patients. The main objective is preventing adverse drug–drug interactions and minimizing the risk of toxic reactions of the several medications utilized by the periodontists.

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