Antiretroviral therapy adherence and drug–drug interactions in the aging HIV population

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It is estimated that by 2015 more than half of all HIV-infected individuals in the United States will be 50 years of age or older. As this population ages, the frequency of non-AIDS related comorbidities increases, which includes cardiovascular, metabolic, gastrointestinal, genitourinary and psychiatric disorders. As a result, medical management of the aging HIV population can be complicated by polypharmacy and higher pill burden, leading to poorer antiretroviral therapy (ART) adherence. Adherence to ART is generally better in older populations when compared to younger populations; however, cognitive impairment in elderly patients can impair adherence, leading to worse treatment outcomes. Practical monitoring tools can improve adherence and increase rates of viral load suppression. Several antiretroviral drugs exhibit inhibitory and/or inducing effects on cytochrome P450 isoenzymes, which are responsible for the metabolism of many medications used for the treatment of comorbidities in the aging HIV population. The combination of ART with polypharmacy significantly increases the chance of potentially serious drug–drug interactions (DDIs), which can lead to drug toxicity, poorer ART adherence, loss of efficacy of the coadministered medication, or virologic breakthrough. Increasing clinicians awareness of common DDIs and the use of DDI programs can prevent coadministration of potentially harmful combinations in elderly HIV-infected individuals. Well designed ART adherence interventions and DDI studies are needed in the elderly HIV population.

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Introduction

The introduction of effective antiretroviral therapy (ART) has resulted in the reduction of AIDS-related mortality [1,2] and increased the life expectancy of HIV-infected individuals [3]. By 2015, it is projected that more than 50% of all HIV-infected individuals living in the United States will be 50 years of age or older [4]. With increasing age, the pattern of morbidity and mortality shifts from AIDS-related opportunistic infections to age-related comorbidities, such as cardiovascular disease, metabolic disorders, non-HIV-related malignancies, osteoporosis and decline in organ function (renal as well as hepatic) [2,5]. When controlling for sex, baseline CD4 cell count and year of therapy initiation, older age (50 years of age and older) was significantly associated with higher mortality [adjusted hazard ratio 1.23, 95% confidence interval (CI) 1.08–1.42] [6]. In addition,

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Goulet *et al.* [7] reported that HIV-infected veterans had a lower risk of hypertension, diabetes, vascular disease and psychiatric disorders. However, they had a higher risk of liver disease, renal disease, substance use disorder and multimorbidity. HIV infected veterans 50 years of age and older had higher odds of multimorbidity than HIV uninfected veterans 50 years of age and older.

Due to the above comorbidities, medical management of older HIV-infected individuals becomes complicated by polypharmacy. In an analysis of the Swiss HIV Cohort study, the combination of ART with polypharmacy significantly increased the chance of potentially serious drug–drug interactions (DDIs) [8], which can lead to drug toxicity, loss of efficacy of the coadministered medication and virologic breakthrough. When HIV-infected individuals at least 50 years of age were compared to HIV-infected individuals less than 50 years of age, older patients were more likely to receive concomitant medications versus younger patients (82 vs. 61%, $P < 0.001$), therefore, also had more DDIs (51 vs. 35%, $P < 0.001$). Certain therapeutic classes were prescribed more often in elderly patients, including cardiovascular drugs, gastrointestinal medications and hormonal agents. Elderly patients are two to three times more likely to develop an adverse drug reaction compared to younger patients [9]. There is a paucity of clinical and pharmacokinetic DDI studies in the older HIV population. In a cohort study of 1000 HIV-negative elderly patients more than 70 years old who were admitted to the hospital for an acute illness, 894 were receiving at least two medications. Of these 894 patients, 60.2% were exposed to potential DDI, and as a result of these DDI, 24% developed clinically significant side effects [10].

Other important ART considerations in the aging HIV population include issues related to adherence, as well as clinical/immunological response to ART. Poor adherence to ART in the aging HIV population can be the consequence of multiple factors including neurocognitive decline [11–13], social isolation/lack of social support and depression [14–17] and chronic adverse drug effects (e.g. lipodystrophy) [18]. High drug cost in uninsured or underinsured elderly patients is also associated with decreased adherence and poor outcome [19,20]. As an example, in the North American AIDS Cohort Collaboration on Research and Design cohort, it was found that older age (per 10 years increment) was associated with a 68% increase in death when ART was deferred [21,22] and that CD4 cell count at presentation for HIV care among patients older than 50 years old were lower [23]. Although elderly patients may have a higher baseline HIV viral load and lower CD4 cell count, their virologic response to ART is similar to younger HIV-infected individuals [24] but CD4 cell recovery after starting ART is generally lower in this elderly HIV-infected population [21,24,25]. However, these findings were not confirmed by Tumbarello *et al.* [26]. Among other factors, biological factors that negatively influence the risk of developing immune responses and immune reconstitution (e.g. advanced diseases at start of ART, thymic output, reduced bone marrow capacity) may affect outcome in the older HIV-infected patients [27–29].

HIV treatment adherence in the aging population

Overall, higher adherence to ART is associated with older age, and although current combination ART can be forgiving of occasional lapses in adherence, higher levels of adherence is associated with the maximal likelihood of virologic suppression and lower level of drug resistance in both younger adults and older patients [30–32]. However, among older patients with HIV, those with documented cognitive decline are likely to have poor ART adherence, disease progression and death [33]. In a volunteer sample of 431 HIV-infected adult patients on ART, recruited from community agencies and university-affiliated infectious disease clinics in the Los Angeles area, neurocognitive measurements were conducted. These included tests on attention, information processing speed, learning/memory, verbal fluency, motor functioning and executive functioning. Medication adherence was measured using microchip-embedded pill bottle caps (Medication Event Monitoring System caps) and was self-reported. Structural equation modeling (SEM) techniques were used to evaluate factor models of cognition and adherence. The study found that mean adherence rates were higher among older ($\geq$50 years) than younger ($<$50 years) HIV-positive adults. Nevertheless, the SEM analysis revealed that older patients with neurocognitive impairment were associated with poorer medication adherence [23]. When cognitive functions were examined individually, executive function, motor function and processing speed were most strongly correlated with adherence in this elderly group. Similar to younger patients, older HIV-positive individuals with neurocognitive impairment or drug abuse problems are at increased risk of suboptimal adherence to medications.The above findings highlight the importance of optimizing medication adherence rates and evaluating neurocognition in the growing population of elderly HIV-infected patients.

In 2008, Branas *et al.* [34] also found that older age was associated with higher ART adherence, however, the authors did not investigate neurocognition disorders as independent factors. In addition, they found a lower CD4 cell count increase after ART initiation in the older group. Hinkin *et al.* [33] found that in addition to neurocognition disorders, current drug abuse or

dependence, but not current alcohol abuse or dependence, was also associated with suboptimal medication adherence.

Antiretroviral therapy adherence interventions in the aging HIV population

There are limited interventional studies aimed to improve ART adherence in the elderly HIV population to guide or support specific recommendations. Although one could extrapolate from other interventions conducted in elderly patients affected by chronic conditions such as diabetes or hypertension, it is important to evaluate such interventions in the aging HIV population and more specifically those with neurocognition disorders and/or drug abuse. ART adherence interventions that have proven effective in the adult HIV-infected population includes electronic reminder devices [35,36], screening for and treating depression [37], addressing substance abuse [38], organizing pillboxes [39], increasing social support [40] and simplifying ART regimens by reducing pill burden and frequency (e.g. once-daily and one tablet fixed-dose combinations) [41]. These interventions are likely to be of value in the elderly HIV population, but specific data in this aging population are urgently needed.

Immunologic and clinical response to antiretroviral therapy in the aging HIV population

HIV-infected patients over the age of 50 are more likely to present with lower CD4 cell counts and more advanced disease [23]. As a result, among patients who are older than 60 years of age, a higher proportion of these patients progressed to AIDS within 1 year of HIV diagnosis compared to younger patients (52 vs. 15%) [42].

Although older HIV-infected individuals are less likely to experience treatment failure with ART compared to younger patients due to better adherence, some studies suggest that older individuals have less CD4 cell recovery [43,44]. In a Spanish study, Nogueras *et al.* [24] showed that although HIV-infected older patients were more likely to have higher viral load and lower CD4 cell counts at baseline when presenting to the first clinic visit, they were not likely to achieve the same CD4 cell counts compared with younger individuals. Based on these observations, the Department of Health and Human Services guidelines recommended ART in all patients older than 50 years of age, regardless of CD4 cell count [45]. However, as shown by Tumbarello *et al.* [26], despite having lower baseline CD4 cell count and higher frequency of comorbid conditions, in multivariate analysis, there was no statistically significant difference between older and younger HIV-infected patients regarding viroimmunological response to ART.

Antiretroviral drug–drug interactions in the aging HIV population

The combination of ART with polypharmacy for the management of comorbidities significantly increases the chance of potentially serious DDI, which can lead to drug toxicity and loss of efficacy. The effect of aging on drug metabolism and clearance adds another layer of complexity. Liver volume [46] and hepatic blood flow [47] decrease with increasing age. Comparisons of drug metabolism *in vivo* have been conducted in younger versus older HIV-negative patients. CYP1A2 activity seems to be preserved in older patients, particularly those who are nonsmokers [48]. Age does not seem to affect CYP2D6 metabolism, whereas CYP2D6 polymorphisms were found to significantly impact elimination rates[49]. The following age-related differences in CYP2C19 metabolism have been noted; older individuals who are either extensive metabolizers or intermediate metabolizers have approximately two-fold higher exposures to omeprazole compared to younger individuals. However, age had less effect on poor metabolizers [50]. Age does not appear to affect CYP2C9 metabolism of diclofenac and celecoxib [51]; however, warfarin is primarily metabolized through CYP2C9, and it has been shown that the average dose requirement for warfarin decreases as age increases [52]. Lastly, age has not been shown to significantly influence CYP3A metabolism [53] even in patients up to 100 years old [54]. This is important because CYP3A enzymes are involved in the metabolism of a majority of medications, and are the basis of many clinically important DDIs between ART and medications commonly prescribed in the aging population. These studies suggest that the overall hepatic elimination through CYP450 enzymes is relatively stable with increasing age. Similarly, phase II metabolism (glucuronidation, acetylation, and sulfatation) is also well preserved in older patients [55]. Enzyme induction also appears to be conserved in older patients, as rifampin was capable of inducing phase I and phase II pathways of metabolism to the same extent as in younger individuals [56].

On average, glomerular filtration declines by 1% per year [57]. HIV-infected patients are at increased risk for developing chronic kidney disease (CKD) with a prevalence of an estimated glomerular filtration rate less than 60 ml/min per 1.73 m^2 reported in approximately 7% of HIV-infected patients [58]. In addition to older age, many other factors such as diabetes, hypertension, intravenous drug use, high viral load, low CD4 cell count, race, concurrent use of certain antiretrovirals [e.g. tenofovir, indinavir, atazanavir (ATV)] and hepatitis C coinfection have been associated with CKD in HIV-infected

individuals [58–61]. In a large cohort study from the Veteran Health Administration involving over 10 000 HIV-infected patients, tenofovir use was associated with a 34% increased risk of proteinuria (95% CI 25–45%, $P < 0.0001$), 11% increased risk of rapid decline in kidney function (95% CI 3–18%, $P = 0.0033$), and 33% increased risk of CKD (95% CI 18–51%; $P < 0.0001$). Risk of tenofovir-associated nephrotoxicity did not further increase in a subgroup of patients older than 46 years [62]. However, in an expanded-access tenofovir study, older age was a baseline risk factor for increased serum creatinine [63]. It is important for clinicians to recognize that older HIV-infected patients may have decreased glomerular filtration rate, and as a result may be at higher risk of nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)-induced toxicity if renal dosing guidelines are not followed [45].

Clinically significant DDI involving ART and medications used to treat cardiovascular diseases, metabolic, gastrointestinal, psychiatric disorders and other medications commonly used in the elderly population are reviewed here with recommendations provided for the selection of alternative agents to minimize potentially harmful DDI. As a class effect, protease inhibitors are inhibitors of CYP450 3A4 enzymes and to some extent of other isoenzymes, with the most potent being ritonavir (RTV), which is used to 'boost' the effect of other protease inhibitors by inhibiting their metabolism. Interactions between protease inhibitors and other medications metabolized through CYP450 may lead to increased plasma concentrations of the coadministered medication, potentially leading to serious/life-threatening adverse drug reactions. With the exception of delavirdine (DLV) and rilpivirine, nonnucleoside reverse transcriptase inhibitors (NNRTIs) including efavirenz (EFV), etravirine (ETR) and nevirapine (NVP) are moderate inducers *in vivo* of CYP450 3A4 enzymes, although EFV has been found *in vitro* to inhibit certain CYP450 enzymes as well [64]. Interactions involving EFV, NVP and ETR and other medications metabolized through CYP450 3A4 can lead to decreased plasma concentrations of the coadministered medication, potentially leading to decreased efficacy. NRTIs, maraviroc, raltegravir, rilpivirine and enfuvirtide do not inhibit or induce CYP450 isoenzymes; therefore, clinically significant DDI are uncommon.

Drug–drug interactions with cardiovascular medications

Cardiovascular disease is one of the most common comorbidities in the aging HIV-infected population [8]. Coronary artery disease (CAD) is emerging as a complication in HIV-infected patients, which may be due to a combination of increasing age, toxicity from long-term ART [65] and potentially due to HIV immune activation. Prolonged treatment with ART is associated with a higher prevalence of hypertension in HIV-infected individuals [66]. Routine blood pressure monitoring and initiation of antihypertensive medications when indicated is essential to decrease the risk of developing hypertension-related morbidities [67]. DDI studies involving cardiovascular agents and antiretroviral drugs were conducted in young healthy volunteers. All dihydropyridine calcium channel blockers (CCBs) are metabolized via CYP3A4; as a result, all boosted protease inhibitors may increase CCB serum concentrations and can potentially prolong the PR interval and augment hypotensive effect. In a drug interaction study conducted with unboosted ATV, diltiazem area under the plasma concentration time curve (AUC) was increased by 225% and the PR interval was prolonged although the majority of patients were asymptomatic with first degree atrioventricular block [68]. Therefore, it is recommended to decrease the diltiazem dose by 50% and titrate slowly with close monitoring [69]. Similarly, use of other CCB that are more likely to prolong the PR interval (e.g. verapamil) with boosted protease inhibitors should be closely monitored. On the contrary, EFV, ETR and NVP have the potential to decrease CCB serum concentrations and dose adjustment of CCB at steady state may be needed. Digoxin serum concentrations were increased by 86% with RTV coadministration due to inhibition of P-glycoprotein (P-gp). [70]. In a cohort study involving 2030 HIV-negative elderly patients who were taking digoxin, if they had been hospitalized during the previous 2 months, they were at more than four times increased risk for additional hospitalizations due to digoxin toxicity [71]. With the increased risk of CKD and potential for DDI with boosted protease inhibitors, HIV-infected elderly patients may be at even higher risk for digoxin toxicity. Close monitoring of digoxin serum concentrations is critical in older HIV-infected patients.

Many antiarrhythmic medications are CYP450 3A4 substrates. The use of amiodarone, bepridil, flecainide, propafenone and quinidine are contraindicated with RTV boosted protease inhibitors (PI/r) due to the potential risk of exacerbating cardiac arrhythmias [72]. The use of disopyramide, dofetilide, lidocaine, mexiletine and procainamide with PI/r should be approached with caution due to the potential risk of significantly increasing antiarrhythmic serum concentrations.

Drug–drug interactions with anticoagulation

Older age is associated with increased risk of major hemorrhage when taking warfarin [73]. Significant DDIs between warfarin, protease inhibitors and NNRTIs may further increase the risk of significant hemorrhage.

Clinically relevant DDIs between anticoagulants and antiretrovirals are listed in Table 1 [69,74,75]. Warfarin exists as two isomers that differ in potency and route of metabolism. S-warfarin is two to five times more potent than R-warfarin. The more potent S-isomer is a CYP2C9 substrate, whereas the R-isomer is metabolized via CYP1A2 and CYP3A4 [76,77]. Induction properties of NVP and lopinavir/RTV at steady state resulting in increased warfarin requirements have been reported [78]. RTV is a mixed CYP3A4 inhibitor and inducer and a mild CYP2C9 inhibitor. When RTV is added to a stable warfarin regimen, a supratherapeutic international normalized ratio (INR) may result initially. However, at steady state, subtherapeutic warfarin concentrations as a result of CYP3A4 induction may occur [79–81]. Although these early reports used higher than currently recommended doses of RTV, a 29% decrease in mean S-warfarin AUC was also observed with darunavir/RTV (DRV/r; 600/100 mg twice daily) [82]. In older patients, close INR monitoring should be performed when boosted protease inhibitors or NNRTIs are added to a stable warfarin regimen.

Dabigatran is a P-gp substrate, but not a substrate, inhibitor or inducer of CYP450 isoenzymes. Certain P-gp inhibitors (e.g. ketoconazole, dronedarone) increase dabigatran concentrations by approximately two-fold [75]. PI/r may inhibit P-gp and may increase dabigatran concentrations. Although clinical data are lacking, in patients with moderate renal impairment (creatinine clearance 15–30 ml/min), a lower dose of dabigatran should be considered in patients treated with boosted protease inhibitors.

Drug–drug interactions with medications used in metabolic disorders

Significant DDI between antiretrovirals and antihyperlipidemic agents have been reported (Table 2) [64,72,83–92]. PI/r can significantly increase simvastatin and lovastatin concentrations. Coadministration of these 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors are not recommended due to the potential for rhabdomyolysis [87,88,92]. Moderate DDIs have been reported with protease inhibitors and atorvastatin [83–86], pravastatin [64,82,89] and rosuvastatin [90], but with close monitoring and dose adjustment, these 'statins' can be safely coadministered with protease inhibitors.

The incidence of T2DM is increased in older HIV-infected individuals, which may be linked to long-term use of ART [93,94]. Non-HIV infected elderly patients 65 years or older with diabetes were found to have a 36% increased risk of developing hypoglycemia while receiving sulfonylureas when compared with younger patients [95]. This risk of hypoglycemia may be even higher in HIV-infected elderly patients due to the presence of DDI between oral hypoglycemics and antiretrovirals. There are limited DDI studies conducted with antiretroviral drugs and oral hypoglycemic medications; however, based on the route of metabolism, there are some potentially significant DDIs [69]. PI/r may increase serum concentrations of sulfonylureas [96,97], pioglitazone [98], repaglinide [99,100] and nateglinide [101]; on the contrary, EFV, ETR and NVP may decrease concentrations of these agents. Rosiglitazone can be considered as an alternative agent with less potential for DDI with antiretrovirals [102,103]. Although DDI are unlikely to occur with metformin through CYP450 enzymes [104], declines in renal function due to increasing age, antiretrovirals (e.g. tenofovir [105]) or HIV-associated nephropathy (HIVAN) [106] can alter the serum concentration of metformin, predisposing to serious side effects including lactic acidosis [107]. Interactions with α-glucosidase inhibitors (acarbose, miglitol) and antiretrovirals are unlikely [108,109]. Among the dipeptidyl peptidase IV inhibitors, the saxagliptin dose should be limited to 2.5 mg once daily when coadministered with PI/r due to inhibition of CYP3A4-mediated metabolism of saxagliptin [110], and linagliptin coadministration with

Table 1. Drug–drug interactions with antiplatelet and anticoagulant agents.

	Drug interaction with antiretrovirals	Management recommendations	References
Aspirin	Interaction with ARVs unlikely	Use standard dose	[69]
Clopidogrel	ETR may decrease the formation of active clopidogrel metabolite. Interaction unlikely with: PI/r, NVP, EFV, RPV, RAL, MVC, NRTIs	Coadministration of clopidogrel with ETR is not recommended.	[74]
Dabigatran	PI/r may increase dabigatran concentrations in patients with moderate to severe renal dysfunction; Interaction unlikely with: NNRTIs, RAL, MVC, NRTIs	With PI/r coadministration, Consider dose reduction with CrCL 30–50 ml/min. Avoid with CrCL <30 ml/min	[75]
Heparin and low molecular weight heparin (LMWH)	Interaction with ARVs unlikely	Use standard dose	[69]
Warfarin	DRV/r, LPV/r, NVP, EFV may decrease S-warfarin concentrations at steady state.	Monitor INR closely with PI/r and NNRTI coadministration.	[69]

ARV, antiretroviral; CrCL, creatinine clearance; DRV/r, darunavir/ritonavir; EFV, efavirenz; ETR, etravirine; INR, international normalized ratio; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NRTI, Nucleoside Reverse Transcriptase Inhibitors; NNRTIs, Non-Nucleoside Reverse Transcriptase Inhibitors; NVP, nevirapine; PI/r, boosted PI; RAL, raltegravir; RPV, rilpivirine.

Table 2. Drug–drug interactions with antihyperlipidemic agents.

	Drug interaction with antiretrovirals	Management recommendations	References
Atorvastatin	Atorvastatin AUC ↑ 2.5, 5.8, and 9.4-fold with FPV/r, LPV/r, and TPV/r coadministration. Atorvastatin AUC ↓ 43% with EFV co-administration.	Avoid TPV/r with atorvastatin coadministration. Other PI/r: start with atorvastatin 10 mg once daily, and then titrate to effect. Do not exceed atorvastatin 20 mg with DRV/r, FPV/r, SQV/r. EFV, NVP, ETR: higher atorvastatin dose may be needed.	[83–86]
Lovastatin	Strong CYP3A4 inhibitor (e.g. itraconazole) significantly increases lovastatin concentrations 20-fold. PI/r may also significantly increase lovastatin concentrations.	PI/r: contraindicated	[72,87]
Pitavastatin	DRV/r and LPV/r decrease pitavastatin AUC 26 and 20%, respectively. ATV increases pitavastatin AUC 31%.	PI/r: use standard dose	[88]
Pravastatin	SQV/r and EFV decrease pravastatin AUC 50 and 40%, respectively. LPV/r and DRV/r increase pravastatin AUC 33% and 81%, respectively.	Higher pravastatin dose may be needed with SQV/r and EFV co-administration. With DRV/r coadministration, use with close monitoring for adverse events.	[64,82,89]
Rosuvastatin	TPV/r, LPV/r, ATV/r increase rosuvastatin AUC 37, 110, and 213%, respectively.	PI/r: start with rosuvastatin 5 mg once daily, then titrate to effect. Maximum recommended rosuvastatin dose 10 mg/day with LPV/r and ATV/r co-administration.	[90,91]
Simvastatin	SQV/r increases simvastatin AUC 31-fold. EFV decreases simvastatin AUC 58%.	PI/r: contraindicated; EFV, NVP, ETR: higher simvastatin dose may be needed.	[72,92,86,89]

ATV, atazanavir; ATV/r, atazanavir/ritonavir; AUC, area under the plasma concentration time curve; DRV/r, darunavir/ ritonavir; EFV, efavirenz; ETR, etravirine; FPV/r, fosamprenavir/ritonavir; LPV/r, lopinavir/ritonavir; NVP, nevirapine; PI/r, protease inhibitor /ritonavir; TPV/r, tipranavir/ritonavir; SQV/r, saquinavir/ritonavir.

PI/r, EFV, ETR and NVP should be avoided [111]. Providers can consider using sitagliptin as an alternative agent [112]; however, close monitoring of blood glucose is recommended.

Drug–drug interactions with medications used for genitourinary disorders

The prevalence of benign prostatic hyperplasia (BPH) is higher in elderly patients. Biopsy confirmed BPH increases from about 40 to 50% in men aged 51–60, to over 80% in men older than 80 years [113]. DDI with BPH medications and antiretroviral drugs are shown in Table 3 [46,69, 114–118]. PI/r may significantly increase concentrations of α-adrenergic antagonist such as alfuzosin and coadministration is not recommended [114]. Tamsulosin is a CYP3A4 and CYP2D6 substrate and its concentrations were increased 2.8-fold when coadministered with a strong CYP3A4 inhibitor (e.g ketoconazole) [115]. Similarly, other PI/r may increase tamsulosin concentration and increase the risk of orthostatic hypotension (especially with the first dose). However, minimal interactions are expected between protease inhibitors and other α antagonists (e.g. doxazosin, prazosin).

Erectile dysfunction has been reported in up to 74% of HIV-infected men [119]. The increased risks are multifactorial and include low testosterone, older age, diabetes, neuropathy, drug use and depression [120]. There are significant DDI between PI/r and drugs used for erectile dysfunction (Table 3). Concentrations of sildenafil [116], tadalafil [117] and vardenafil [118] can all be increased by 2.2–11-fold with PI/r. With PI/r coadministration, dose adjustment of erectile dysfunction agents is recommended to prevent unsafe drop in blood pressure.

Drug–drug interactions with medications used for gastrointestinal disorders

Interactions with acid reducing agents and antiretroviral drugs are common in clinical practice. There have been significant increases seen over time in the frequencies of reflux symptoms, gastroesophageal reflux disease and *Helicobacter pylori* infections in HIV-infected individuals [121]. Additionally, HIV-infected individuals have been found to have elevated gastric pH values, which can lead to alteration in drug absorption [122]. Providers should be aware of clinically significant DDIs with acid-reducing agents and several antiretrovirals including ATV [68,123,124], unboosted fosamprenavir [83], nelfinavir [125], tipranavir [84] and rilpivirine [126]. These antiretroviral drugs require an acidic environment for absorption; therefore, any acid suppressant therapy

Table 3. Drug-drug interactions with genitourinary medications.

	Drug interaction with antiretrovirals	Management recommendations	Reference
Alfuzosin	Alfuzosin concentrations can be significantly increased with PI/r	Contraindicated. Consider tamsulosin	[114]
Tamsulosin	CYP3A4 inhibitor (e.g. ketoconazole) increases tamsulosin AUC 2.8-fold.	With PI/r coadministration, consider tamsulosin dose reduction with the first dose	[115]
Doxazosin, prazosin	Minimal interaction with PI/r expected	Use standard dose with slow titration	[69]
Dutasteride, finasteride	Dutasteride (and to a lesser extent finasteride) concentrations may be increased with PI/r coadministration	Consider finasteride. Monitor for decreased libido and erectile dysfunction.	[46]
Tadalafil, sildenafil, vardenafil	With RTV, tadalafil AUC increased 127%; With RTV, sildenafil AUC increased 11-fold; With IDV, vardenafil AUC increased 16-fold	Start with tadalafil 2.5–5 mg and do not exceed 10 mg in 72 h; do not exceed sildenafil 25 mg q 48 h; do not exceed vardenafil 2.5 mg q 24 h	[116–118]

AUC, area under the plasma concentration time curve; PI/r, protease inhibitor/ritonavir; RTV, ritonavir; IDV, indinavir.

(antacids, H_2 receptor antagonists, proton pump inhibitors) has the potential to significantly reduce these antiretroviral serum concentrations, which can potentially lead to treatment failure of HIV. For example, the coadministration of ATV/RTV (ATV/r) with omeprazole resulted in a 76% decrease in ATV AUC [68]. Although the manufacturer suggests that ATV/r can be safely coadministered with low-dose (20 mg) omeprazole, most experts recommend switching to an alternative protease inhibitor such as DRV/r. Recommendations for the safe coadministration of these antiretroviral drugs with acid suppressants are summarized in Table 4 [68,69,83, 84,124–126].

Drug–drug interactions with medications used for central nervous system disorders

Depression and other psychiatric conditions are prevalent in HIV-infected patients [12,127–131]. Non-HIV infected elderly patients taking psychotropics, antidepressants and benzodiazepines are at 78, 59 and 39% increased risk for fall, respectively [132]. However, treatment of depression is critical in the elderly HIV population because untreated depression negatively impacts progression to AIDS and death in patients with HIV [133]. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for depression in HIV-infected individuals [134], as they are better tolerated than tricyclic antidepressants (TCA). With protease inhibitor coadministration, orthostatic hypotension and anticholinergic side effects from TCAs can result in severe morbidity [72]. There are also several clinically significant DDI with other antidepressants that warrant a dosage reduction of the antidepressant listed in Table 5 [64,69,72,82,126, 135–153,156–163]. In general, the SSRIs including escitalopram and citalopram are preferred in HIV-infected patients requiring antidepressant therapy due to less potential for DDI with antiretrovirals [69].

The prevalence of HIV among psychiatric patients has been reported to range from 8 to 19% [164,165], and a significant proportion of patients with schizophrenia engage in high-risk sexual behaviors that increase the risk of acquiring HIV [166]. Atypical antipsychotics are preferred over conventional (typical) antipsychotics in the elderly population [167], but studies specific to the HIV population are lacking. The atypical antipsychotics are associated with undesired metabolic effects (hyperglycemia, hypercholesterolemia) [168], and coadminsitration with antiretroviral drugs that also increase risk of metabolic effects (e.g. protease inhibitors and hyperlipidemia) [169] can potentially increase the risk of cardiovascular diseases in HIV-infected individuals. Several antipsychotics have significant DDI with antiretrovirals and dosage reduction of the antipsychotic may be required (Table 5).

Drug–drug interactions with osteoporosis medications

The prevalence of osteoporosis in HIV-infected individuals has been found to be three-fold higher compared with HIV-negative individuals [170], and the overall prevalence of patients with fracture was found to be 2.87 vs. 1.77 per 100 persons in HIV-infected vs. HIV-uninfected individuals ($P < 0.0001$) [171]. Tenofovir-containing antiretroviral regimens have been associated with larger decrease in spine and hip bone mineral density when compared with abacavir-containing regimens [172]. ATV/r and EFV have also been found to be associated with a decrease in spine and hip bone mineral density [173]. First-line therapy for osteoporosis consists of bisphosphonates, which have been demonstrated to be efficacious in patients with HIV-associated osteoporosis [174], and there are no known DDI between bisphosphonates and antiretrovirals. Calcium and vitamin D supplementation is often recommended for bone health,

Table 4. Drug–drug interactions with acid suppressants.

	Antiretroviral	Drug interaction with antiretrovirals	Management recommendations	References
Antacids (any aluminum, calcium, or magnesium containing products)	Atazanavir, tipranavir, and rilpivirine	Antacids can decrease ARV serum concentrations	Can give atazanavir ≥2 h before OR 1 h after antacids or buffered medications. Can give tipranavir ≥2 h before OR 1 h after antacids. Can give antacids ≥2 h before OR ≥4 h after rilpivirine.	[68,69,84,126]
H2 receptor antagonist (H2RA): cimetidine, famotidine, nizatidine, ranitidine	Boosted atazanavir (ATV/r)	Famotidine 40 mg b.i.d. given with ATV/r (300/100 mg daily) resulted in 18% decrease in ATV AUC	If need to coadminister ATV/r with H2RA, should not exceed dose equivalent to famotidine 40 mg b.i.d. in treatment-naive patients, or famotidine 20 mg b.i.d. in treatment-experienced patients. Give ATV/r (300/100 mg) ≥10 h after the H2RA.	[68]
	Boosted atazanavir (ATV/r) with tenofovir (TDF)	Famotidine 40 mg b.i.d. with ATV/r (300/100 mg) and TDF resulted in 21% decrease in ATV AUC, despite spacing apart of doses	If using ATV/r with TDF and H2RA in treatment experienced patient, increase dose of ATV/r to 400/100 mg once daily, and do not exceed dose equivalent to famotidine 20 mg b.i.d. Give ATV/r (400/100 mg) ≥10 h after the H2RA.	[68]
	Unboosted atazanavir (ATV)	Famotidine 40 mg b.i.d. given with ATV 400 mg daily resulted in 41% decrease in ATV AUC	If need to coadminister ATV with H2RA, should not exceed dose equivalent of famotidine 20 mg/dose and not exceed total daily dose of famotidine 20 mg b.i.d. in treatment-naive patients. Give ATV ≥2 h before OR ≥10 h after H2RA.	[68]
	Fosamprenavir, tipranavir, and rilpivirine	H2RA can decrease ARV serum concentrations.	Give FPV/r (700/100 mg b.i.d.) 2 h before H2RA. Although no DDI data, consider administration of H2RA 2 h after tipranavir. H2RA must be given ≥12 h before OR ≥4 hrs after rilpivirine.	[69,83,126]
Proton pump inhibitor (PPI): Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Boosted atazanavir (ATV/r)	Omeprazole 40 mg daily with ATV/r (300/100 mg daily) resulted in 76% decrease in ATV AUC. With omeprazole 20 mg daily with ATV/r (300/100 mg daily), ATV AUC decreased 42%, and increasing the ATV/r dose to 400/100 mg daily resulted in 30% decrease in ATV AUC.	Coadministration not recommended; consider an alternative PI such as DRV/r, LPV/r or FPV/r. If need to coadminister ATV/r with PPI, should not exceed dose equivalent to omeprazole 20 mg daily in treatment-naive patients; Give PPI ≥12 h before ATV/r. PPI not recommended in treatment experienced patients on ATV/r. PPI not recommended with unboosted atazanavir.	[68,124]
	Nelfinavir	Omeprazole 40 mg daily decreased nelfinavir and M8 active metabolite AUC by 37 and 89%, respectively	PPI not recommended with nelfinavir.	[125]
	Rilpivirine	Omeprazole 20 mg daily decreases rilpivirine AUC 40%.	PPI contraindicated with rilpivirine.	[126]

ARV, antiretroviral; ATV/r, atazanavir/ritonavir; ATV, atazanavir; AUC, area under the plasma concentration time curve; DRV/r, darunavir/ritonavir; FPV/r, fosamprenavir/ritonavir; LPV/r, lopinavir/ritonavir; PI, protease inhibitor; TDF, tenofovir; BID, twice daily; H2RA, H2 Receptor Antagonists; PPI, proton pump inhibitors; DDI, drug–drug interaction.

Table 5. Drug–drug interactions with antidepressants / antipsychotics.

Drug class	Drug interaction with antiretrovirals	Management recommendations	References
Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	DRV/r decreased paroxetine AUC 39%, and FPV/r decreased paroxetine AUC 55%. Boosted PIs may increase fluoxetine concentrations, and NVP can decrease fluoxetine concentrations. EFV and DRV/r decrease sertraline AUC by 39 and 49%, respectively.	Titrate SSRI to effect. Escitalopram and citalopram are preferred SSRIs.	[64,69,82,135–139]
SSRI/5-HT1A receptor partial agonist: vilazodone	Ketoconazole (CYP3A4 inhibitor) increased vilazodone concentrations ~50%. Boosted PIs may increase vilazodone concentrations.	If coadminister with boosted PI, reduce vilazodone dose to 20 mg once daily.	[140]
Serotonin–norepinephrine reuptake inhibitors (SNRIs): duloxetine, venlafaxine, desvenlafaxine	DRV/r may increase concentration of duloxetine. High-dose RTV, LPV/r, and TPV/r may decrease duloxetine concentrations at steady state. Boosted PIs may increase venlafaxine concentrations, whereas EFV, ETR, and NVP may decrease venlafaxine concentrations. Ketoconazole (CYP3A4 inhibitor) increased desvenlafaxine AUC 43%. Boosted PIs may increase desvenlafaxine concentrations.	Titrate to effect, or consider an alternative antidepressant (e.g. SSRIs)	[69,141–144]
Noradrenergic antagonist: mirtazapine	Ketoconazole (CYP3A4 inhibitor) increased mirtazapine AUC 50%. Boosted PIs may increase mirtazapine concentrations.	If coadminister with boosted PIs, start with 15 mg at bedtime. Titrate to effect. Also promotes increased appetite and weight gain which is beneficial in HIV-associated wasting syndrome.	[69,145,146]
Serotonin reuptake inhibitor/ antagonist: trazodone	RTV 200 mg b.i.d. increased trazodone AUC 2.4 fold, and resulted in nausea, dizziness, hypotension, and syncope.	Use with caution with boosted PIs, and start at 50% of standard dose of trazodone (for LPV/r, use lowest trazodone dose with slow titration). Monitor for nausea, dizziness, hypotension, and syncope. SQV/r contraindicated with trazodone due to risk of additive QT-prolongation. Consider alternative antidepressant (e.g. SSRIs)	[69,147,148]
Serotonin reuptake inhibitor/ antagonist: nefazodone	Boosted PIs may increase nefazodone concentrations. Maraviroc AUC may be increased by nefazodone.	Use with caution with boosted PIs, and start at 50% of standard dose. Consider alternative antidepressant (e.g. SSRIs). Decrease maraviroc dose to 150 mg b.i.d. with nefazodone coadministration.	[69,72,149]
Dopamine-reuptake inhibitor: bupropion	LPV/r decreased bupropion AUC 57%. TPV/r decreased bupropion AUC 49%. EFV decreased bupropion AUC 55%; ETR may decrease bupropion serum concentrations. NFV may increase bupropion concentration, but no seizures observed.	If co-administer with LPV/r, TPV/r, EFV, or ETR, monitor for bupropion therapeutic efficacy; bupropion dose may need to be adjusted. If coadminister with NFV start with the lowest possible dose of bupropion.	[69,150–153]
Tricyclic Antidepressant (TCA): amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline	Desipramine AUC increased 145% with RTV 500 mg b.i.d. coadministration.	Use low dose TCA with PI coadministration or consider alternative antidepressant (e.g. SSRIs). Monitor closely for TCA toxicity. Avoid rilpivirine coadministration with TCA due to risk of additive QT-prolongation.	[69,72,126]

Table 5 (*continued*)

Drug class	Drug interaction with antiretrovirals	Management recommendations	References
Atypical antipsychotics: aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone	Ketoconazole (CYP3A4 inhibitor) increased aripiprazole AUC by 63%, and quinidine (CYP2D6 inhibitor) increased aripiprazole AUC by 112%. A combination of DRV/r, duloxetine, and aripiprazole resulted in a 5-fold increase in aripiprazole concentration. Carbamazepine (3A4 inducer) decreased aripiprazole AUC by 70%. PIs may increase quetiapine, risperidone, iloperidone, and ziprasidone concentrations; EFV, ETR, NVP may decrease quetiapine, risperidone, iloperidone, and ziprasidone concentrations; Reversible toxic coma has been reported with indinavir/ritonavir and risperidone coadministration. RTV decreased olanzapine AUC by 53%.	If coadminister aripiprazole with boosted PI, decrease aripiprazole dose by 50%. If coadminister aripiprazole with boosted PI and a concomitant CYP2D6 inhibitor (e.g. quinidine, fluoxetine, or paroxetine), decrease aripiprazole dose to 25% of usual dose; If co-administer aripiprazole with EFV, ETR, or NVP, aripiprazole dose may need to be increased. If coadminister quetiapine, iloperidone, or risperidone with boosted PIs, reduce dose of antipsychotic, or use alternative antipsychotic (e.g. olanzapine); Avoid PIs with ziprasidone; may increase risk of QT-prolongation	[69,154–162]
Typical antipsychotics: chlorpromazine, fluphenazine, haloperidol, perphenazine, pimozide, thioridazine	Boosted PIs may increase serum concentrations of typical antipsychotics; EFV, ETR, and NVP may decrease serum concentrations of typical antipsychotics	If coadministered with PIs, use with close monitoring for antipsychotic associated adverse drug reaction. Consider alternative antipsychotic such as olanzapine. Pimozide is contraindicated with PIs due to risk of QT-prolongation. Avoid rilpivirine coadministration with typical antipsychotics due to risk of additive QT-prolongation.	[69,163]

AUC, area under the plasma concentration time curve; PI, protease inhibitor; DRV/r, darunavir/ritonavir; FPV/r, fosamprenavir/ritonavir; LPV/r, lopinavir/ritonavir; TPV/r, tipranavir/ritonavir; SQV/r, saquinavir/ritonavir; RTV, ritonavir; NFV, nelfinavir; EFV, efavirenz; ETR, etravirine; NVP, nevirapine.

and significant DDI with calcium-containing products and several antiretrovirals are outlined in Table 4.

Conclusion

Management of ART in the aging HIV population is a therapeutic challenge from many different perspectives. With increasing age, patterns of comorbidities are shifting to cardiovascular disorders, metabolic disorders, gastrointestinal/genitourinary disorders and psychiatric disorders. Treatment of these comorbidities introduces polypharmacy, increasing the risk of clinically significant DDIs, which can lead to adverse effects or treatment failure of HIV. Although adherence tends to be higher in older individuals compared to younger individuals, cognitive impairment can impair adherence, leading to worse treatment outcomes. Also, polypharmacy can contribute to medication fatigue. Healthcare providers caring for the elderly HIV population should communicate to their patients the critical need for adherence to ART, its short-term and long-term benefits and provide them with practical monitoring tools to achieve high adherence levels for maximum viral suppression, halt of disease progression and increase in quality of life. There is a need for targeted interventions to improve ART adherence in the aging HIV population. Screening and management for other age-related comorbidities (e.g. diabetes, high blood pressure), depression, cognitive decline and substance abuse should be a top priority. Several antiretroviral drugs exhibit inhibitory (protease inhibitors, DLV) and inducing (EFV, ETR, NVP) effects on CYP450 isoenzymes, which are responsible for the metabolism of many medications used for the treatment of comorbidities in the aging HIV population. Awareness of common DDI among elderly HIV-infected individuals are important to help prevent them and assure long-term success of ART. Healthcare providers should routinely screen patients' medication lists to look for significant DDIs and perform drug interaction checks using available online resources (e.g. http://www.hopkins-hivguide.org, http://www.clinicaloptions.com and http://www.hiv-druginteractions.org) prior to the initiation of new medications in HIV-infected individuals on ART. Although there are many drug interaction studies documenting significant DDIs between antiretroviral drugs and medications that are commonly prescribed in the elderly population, the majority of these pharmacokinetic studies were conducted in young, healthy volunteers who are not HIV-infected. As a result, these studies may not be generalizable to elderly HIV-infected patients. There is a need for investigations specifically in HIV-infected individuals, including those who are elderly.

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Conflicts of interest

There are no conflicts of interest.

References

1. Valdez H, Chowdhry TK, Asaad R, Woolley IJ, Davis T, Davidson R, *et al*. **Changing spectrum of mortality due to human immunodeficiency virus: analysis of 260 deaths during 1995–1999.** *Clin Infect Dis* 2001; **32**:1487–1493.
2. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis* 2010; **50**:1387–1396.
3. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; **372**:293–299.
4. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, *et al*. **Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions.** *Clin Infect Dis* 2008; **47**:542–553.
5. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, *et al*. **Morbidity and aging in hiv-infected persons: the Swiss HIV cohort study.** *Clin Infect Dis* 2011; **53**:1130–1139.
6. Bakanda C, Birungi J, Mwesigwa R, Ford N, Cooper CL, Au-Yeung C, *et al*. **Association of aging and survival in a large HIV-infected cohort on antiretroviral therapy.** *AIDS* 2011; **25**:701–705.
7. Goulet JL, Fultz SL, Rimland D, Butt A, Gibert C, Rodriguez-Barradas M, *et al*. **Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity?** *Clin Infect Dis* 2007; **45**:1593–1601.
8. Marzolini C, Back D, Weber R, Furrer H, Cavassini M, Calmy A, *et al*. **Ageing with HIV: medication use and risk for potential drug-drug interactions.** *J Antimicrob Chemother* 2011; **66**:2107–2111.
9. Nolan L, O'Malley K. **Prescribing for the elderly. Part I: sensitivity of the elderly to adverse drug reactions.** *J Am Geriatr Soc* 1988; **36**:142–149.
10. Doucet J, Chassagne P, Trivalle C, Landrin I, Pauty MD, Kadri N, *et al*. **Drug-drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients.** *J Am Geriatr Soc* 1996; **44**:944–948.
11. Hardy DJ, Vance DE. **The neuropsychology of HIV/AIDS in older adults.** *Neuropsychol Rev* 2009; **19**:263–272.
12. Hinkin CH, Castellon SA, Atkinson JH, Goodkin K. **Neuropsychiatric aspects of HIV infection among older adults.** *J Clin Epidemiol* 2001; **54 (Suppl 1)**:S44–S52.
13. Kissel EC, Pukay-Martin ND, Bornstein RA. **The relationship between age and cognitive function in HIV-infected men.** *J Neuropsychiatry Clin Neurosci* 2005; **17**:180–184.
14. Kalichman SC, Heckman T, Kochman A, Sikkema K, Bergholte J. **Depression and thoughts of suicide among middle-aged and older persons living with HIV-AIDS.** *Psychiatr Serv* 2000; **51**:903–907.
15. Lima VD, Geller J, Bangsberg DR, Patterson TL, Daniel M, Kerr T, *et al*. **The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART.** *AIDS* 2007; **21**:1175–1183.
16. McGuire LC, Ford ES, Ajani UA. **Cognitive functioning as a predictor of functional disability in later life.** *Am J Geriatr Psychiatry* 2006; **14**:36–42.
17. Shippy RA, Karpiak SE. **The aging HIV/AIDS population: fragile social networks.** *Aging Ment Health* 2005; **9**:246–254.
18. Nachega JB, Trotta MP, Nelson M, Ammassari A. **Impact of metabolic complications on antiretroviral treatment adherence: clinical and public health implications.** *Curr HIV/AIDS Rep* 2009; **6**:121–129.
19. Johnston SS, Juday T, Seekins D, Espindle D, Chu BC. **Association between prescription cost sharing and adherence.** *J Manag Care Pharm* 2012; **18**:129–145.
20. Mishra SI, Gioia D, Childress S, Barnet B, Webster RL. **Adherence to medication regimens among low-income patients with multiple comorbid chronic conditions.** *Health Soc Work* 2011; **36**:249–258.
21. Althoff KN, Justice AC, Gange SJ, Deeks SG, Saag MS, Silverberg MJ, *et al*. **Virologic and immunologic response to HAART, by age and regimen class.** *AIDS* 2010; **24**:2469–2479.
22. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, *et al*. **Effect of early versus deferred antiretroviral therapy for HIV on survival.** *N Engl J Med* 2009; **360**:1815–1826.
23. Althoff KN, Gebo KA, Gange SJ, Klein MB, Brooks JT, Hogg RS, *et al*. **CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation?** *AIDS Res Ther* 2010; **7**:45.
24. Nogueras M, Navarro G, Anton E, Sala M, Cervantes M, Amengual M, *et al*. **Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more.** *BMC Infect Dis* 2006; **6**:159.
25. Sabin CA, Smith CJ, d'Arminio Monforte A, Battegay M, Gabiano C, Galli L, *et al*. **Response to combination antiretroviral therapy: variation by age.** *AIDS* 2008; **22**:1463–1473.
26. Tumbarello M, Rabagliati R, de Gaetano Donati K, Bertagnolio S, Montuori E, Tamburrini E, *et al*. **Older age does not influence CD4 cell recovery in HIV-1 infected patients receiving highly active antiretroviral therapy.** *BMC Infect Dis* 2004; **4**:46.
27. Meintjes G, Rabie H, Wilkinson RJ, Cotton MF. **Tuberculosis-associated immune reconstitution inflammatory syndrome and unmasking of tuberculosis by antiretroviral therapy.** *Clin Chest Med* 2009; **30**:797–810.
28. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White AC Jr, *et al*. **Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy.** *AIDS* 2005; **19**:399–406.
29. Valin N, Pacanowski J, Denoeud L, Lacombe K, Lalande V, Fonquernie L, *et al*. **Risk factors for 'unmasking immune reconstitution inflammatory syndrome' presentation of tuberculosis following combination antiretroviral therapy initiation in HIV-infected patients.** *AIDS* 2010; **24**:1519–1525.
30. Kobin AB, Sheth NU. **Levels of adherence required for virologic suppression among newer antiretroviral medications.** *Ann Pharmacother* 2011; **45**:372–379.
31. Martin M, Del Cacho E, Codina C, Tuset M, De Lazzari E, Mallolas J, *et al*. **Relationship between adherence level, type of the antiretroviral regimen, and plasma HIV type 1 RNA viral load: a prospective cohort study.** *AIDS Res Hum Retroviruses* 2008; **24**:1263–1268.
32. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. **Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes.** *Ann Intern Med* 2007; **146**:564–573.
33. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, *et al*. **Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse.** *AIDS* 2004; **18 (Suppl 1)**:S19–S25.
34. Branas F, Berenguer J, Sanchez-Conde M, Lopez-Bernaldo de Quiros JC, Miralles P, Cosin J, *et al*. **The eldest of older adults living with HIV: response and adherence to highly active antiretroviral therapy.** *Am J Med* 2008; **121**:820–824.
35. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, *et al*. **Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial.** *Lancet* 2010; **376**:1838–1845.

36. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, *et al*. **Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders.** *AIDS* 2011; **25**:825–834.
37. Nakimuli-Mpungu E, Bass JK, Alexandre P, Mills EJ, Musisi S, Ram M, *et al*. **Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review**. *AIDS Behav* 2011. [Epub ahead of print]
38. Altice FL, Bruce RD, Lucas GM, Lum PJ, Korthuis PT, Flanigan TP, *et al*. **HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study.** *J Acquir Immune Defic Syndr* 2011; **56 (Suppl 1)**:S22–S32.
39. Petersen ML, Wang Y, van der Laan MJ, Guzman D, Riley E, Bangsberg DR. **Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis.** *Clin Infect Dis* 2007; **45**:908–915.
40. Uchino BN. **Social support and health: a review of physiological processes potentially underlying links to disease outcomes.** *J Behav Med* 2006; **29**:377–387.
41. Nachega JB, Mugavero MJ, Zeier M, Vitoria M, Gallant JE. **Treatment simplification in HIV-infected adults as a strategy to prevent toxicity, improve adherence, quality of life and decrease healthcare costs.** *Patient Prefer Adherence* 2011; **5**:357–367.
42. Dursun SM, Reveley MA. **Serotonin hypothesis of psychiatric disorders during HIV infection.** *Med Hypotheses* 1995; **44**:263–267.
43. Chao C, Tang B, Hurley L, Silverberg MJ, Towner W, Preciado M, *et al*. **Risk factors for short-term virologic outcomes among HIV-infected patients undergoing regimen switch of combination antiretroviral therapy**. *AIDS Res Hum Retroviruses* 2012. [Epub ahead of print]
44. Nglazi MD, Kranzer K, Holele P, Kaplan R, Mark D, Jaspan H, *et al*. **Treatment outcomes in HIV-infected adolescents attending a community-based antiretroviral therapy clinic in South Africa.** *BMC Infect Dis* 2012; **12**:21.
45. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; pp. 1–239. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Accessed 31 March 2012].
46. Marchesini G, Bua V, Brunori A, Bianchi G, Pisi P, Fabbri A, *et al*. **Galactose elimination capacity and liver volume in aging man.** *Hepatology* 1988; **8**:1079–1083.
47. Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, James OF. **The effect of age upon liver volume and apparent liver blood flow in healthy man.** *Hepatology* 1989; **9**:297–301.
48. Simon T, Becquemont L, Hamon B, Nouyrigat E, Chodjania Y, Poirier JM, *et al*. **Variability of cytochrome P450 1A2 activity over time in young and elderly healthy volunteers.** *Br J Clin Pharmacol* 2001; **52**:601–604.
49. Feng Y, Pollock BG, Ferrell RE, Kimak MA, Reynolds CF 3rd, Bies RR. **Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling.** *Br J Clin Pharmacol* 2006; **61**:558–569.
50. Ishizawa Y, Yasui-Furukori N, Takahata T, Sasaki M, Tateishi T. **The effect of aging on the relationship between the cytochrome P450 2C19 genotype and omeprazole pharmacokinetics.** *Clin Pharmacokinet* 2005; **44**:1179–1189.
51. Brenner SS, Herrlinger C, Dilger K, Murdter TE, Hofmann U, Marx C, *et al*. **Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib.** *Clin Pharmacokinet* 2003; **42**:283–292.
52. Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. **Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population.** *Chest* 2005; **127**:2049–2056.
53. Gorski JC, Vannaprasaht S, Hamman MA, Ambrosius WT, Bruce MA, Haehner-Daniels B, *et al*. **The effect of age, sex, and rifampin administration on intestinal and hepatic cytochrome P450 3A activity.** *Clin Pharmacol Ther* 2003; **74**:275–287.
54. Schwartz JB. **Erythromycin breath test results in elderly, very elderly, and frail elderly persons.** *Clin Pharmacol Ther* 2006; **79**:440–448.
55. Villesen HH, Banning AM, Petersen RH, Weinelt S, Poulsen JB, Hansen SH, *et al*. **Pharmacokinetics of morphine and oxycodone following intravenous administration in elderly patients.** *Ther Clin Risk Manag* 2007; **3**:961–967.
56. Dilger K, Hofmann U, Klotz U. **Enzyme induction in the elderly: effect of rifampin on the pharmacokinetics and pharmacodynamics of propafenone.** *Clin Pharmacol Ther* 2000; **67**:512–520.
57. Clark WF, Sontrop JM, Macnab JJ, Suri RS, Moist L, Salvadori M, *et al*. **Urine volume and change in estimated GFR in a community-based cohort study.** *Clin J Am Soc Nephrol* 2011; **6**:2634–2641.
58. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. **Racial differences in end-stage renal disease rates in HIV infection versus diabetes.** *J Am Soc Nephrol* 2007; **18**:2968–2974.
59. Kalayjian RC, Franceschini N, Gupta SK, Szczech LA, Mupere E, Bosch RJ, *et al*. **Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease.** *AIDS* 2008; **22**:481–487.
60. Mocroft A, Kirk O, Gatell J, Reiss P, Gargalianos P, Zilmer K, *et al*. **Chronic renal failure among HIV-1-infected patients.** *AIDS* 2007; **21**:1119–1127.
61. Tsui J, Vittinghoff E, Anastos K, Augenbraun M, Young M, Nowicki M, *et al*. **Hepatitis C seropositivity and kidney function decline among women with HIV: data from the Women's Interagency HIV Study.** *Am J Kidney Dis* 2009; **54**:43–50.
62. Scherzer R, Estrella M, Li Y, Deeks SG, Grunfeld C, Shlipak MG. **Association of tenofovir exposure with kidney disease risk in HIV infection**. *AIDS* 2012; **26**:867–875.
63. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, *et al*. **The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years.** *AIDS* 2007; **21**:1273–1281.
64. Bristol-Myers Squibb Company. SUSTIVA® (efavirenz) capsules and tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020972s038lbl.pdf. [Accessed 8 December 2011].
65. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, *et al*. **Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study.** *J Infect Dis* 2010; **201**:318–330.
66. Seaberg EC, Munoz A, Lu M, Detels R, Margolick JB, Riddler SA, *et al*. **Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003.** *AIDS* 2005; **19**:953–960.
67. Goldberg D. **Epidemiology of mental disorders in primary care settings.** *Epidemiol Rev* 1995; **17**:182–190.
68. Bristol-Myers Squibb Company. REYATAZ® (atazanavir sulfate) Capsules. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021567s026lbl.pdf. [Accessed 5 December 2011].
69. Pham PA, Flexner C. *Antiretroviral Drug Interactions*. Durham, NC: Knowledge Source Solutions; 2012.
70. Ding R, Tayrouz Y, Riedel KD, Burhenne J, Weiss J, Mikus G, *et al*. **Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers.** *Clin Pharmacol Ther* 2004; **76**:73–84.
71. Haynes K, Hennessy S, Localio AR, Cohen A, Leonard CE, Kimmel SE, *et al*. **Increased risk of digoxin toxicity following hospitalization.** *Pharmacoepidemiol Drug Saf* 2009; **18**:28–35.
72. Abbott Laboratories. NORVIR(R) (ritonavir) tablets and oral solution. Prescribing information [online]. http://www.rxabbott.com/pdf/norvirtab_pi.pdf. [Accessed 8 December 2011].
73. Fang MC, Go AS, Hylek EM, Chang Y, Henault LE, Jensvold NG, *et al*. **Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study.** *J Am Geriatr Soc* 2006; **54**:1231–1236.
74. Tibotec Therapeutics. INTELENCE® (etravirine) [Tablets]. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022187s008lbl.pdf. [Accessed 8 December 2011].

75. Boehringer Ingelheim Pharmaceuticals. PRADAXA® (dabigatran etexilate mesylate) capsules for oral use. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf. [Accessed 17 December 2011].
76. Kaminsky LS, Zhang ZY. **Human P450 metabolism of warfarin.** *Pharmacol Ther* 1997; **73**:67–74.
77. Rettie AE, Korzekwa KR, Kunze KL, Lawrence RF, Eddy AC, Aoyama T, *et al*. **Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-4502C9 in the etiology of (S)-warfarin-drug interactions.** *Chem Res Toxicol* 1992; **5**:54–59.
78. Liedtke MD, Rathbun RC. **Warfarin-antiretroviral interactions.** *Ann Pharmacother* 2009; **43**:322–328.
79. Knoell KR, Young TM, Cousins ES. **Potential interaction involving warfarin and ritonavir.** *Ann Pharmacother* 1998; **32**:1299–1302.
80. Kumar GN, Rodrigues AD, Buko AM, Denissen JF. **Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes.** *J Pharmacol Exp Ther* 1996; **277**:423–431.
81. Newshan G, Tsang P. **Ritonavir and warfarin interaction.** *AIDS* 1999; **13**:1788–1789.
82. Tibotec Pharmaceuticals. PREZISTA (darunavir) Tablet. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021976s018lbl.pdf. [accessed 6 December 2011].
83. ViiV Healthcare. LEXIVA (fosamprenavir calcium) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021548s026,022116s010lbl.pdf. [Accessed 6 December 2011].
84. Boehringer Ingelheim Pharmaceuticals. APTIVUS® (tipranavir) capsules. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021814s011lbl.pdf. [Accessed 6 December 2011].
85. Abbott Laboratories. KALETRA(R) (lopinavir/ritonavir) tablets and oral solution. Prescribing information [online]. http://www.rxabbott.com/pdf/kaletratabpi.pdf. [Accessed 8 December 2011].
86. Gerber JG, Rosenkranz SL, Fichtenbaum CJ, Vega JM, Yang A, Alston BL, *et al*. **Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study.** *J Acquir Immune Defic Syndr* 2005; **39**:307–312.
87. Merck & Co. MEVACOR (LOVASTATIN) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatf da_docs/label/2011/019643s084lbl.pdf. [Accessed 17 December 2011].
88. Kowa Pharmaceuticals America Inc. LIVALO (pitavastatin) Tablet, Film Coated for Oral use. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022363s006lbl.pdf. [Accessed 17 December 2011].
89. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, Segal Y, Aberg JA, Blaschke T, *et al*. **Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047.** *AIDS* 2002; **16**:569–577.
90. Pham PA, la Porte CJ, Lee LS, van Heeswijk R, Sabo JP, Elgadi MM, *et al*. **Differential effects of tipranavir plus ritonavir on atorvastatin or rosuvastatin pharmacokinetics in healthy volunteers.** *Antimicrob Agents Chemother* 2009; **53**:4385–4392.
91. Busti AJ, Bain AM, Hall RG 2nd, Bedimo RG, Leff RD, Meek C, *et al*. **Effects of atazanavir/ritonavir or fosamprenavir/ritonavir on the pharmacokinetics of rosuvastatin.** *J Cardiovasc Pharmacol* 2008; **51**:605–610.
92. Merck & Co. ZOCOR (simvastatin) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019766s083lbl.pdf. [Accessed 17 December 2011].
93. Capeau J, Bouteloup V, Katlama C, Bastard JP, Guiyedi V, Salmon-Ceron D, *et al*. **Ten-year diabetes incidence in 1,046 HIV-infected patients started on a combination antiretroviral treatment: the ANRS CO8 APROCO-COPILOTE cohort**. *AIDS* 2012; **26**:303–314.
94. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, *et al*. **Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study.** *Arch Intern Med* 2005; **165**:1179–1184.
95. van Staa T, Abenhaim L, Monette J. **Rates of hypoglycemia in users of sulfonylureas.** *J Clin Epidemiol* 1997; **50**:735–741.
96. Niemi M, Cascorbi I, Timm R, Kroemer HK, Neuvonen PJ, Kivisto KT. **Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes.** *Clin Pharmacol Ther* 2002; **72**:326–332.
97. Sanofi-Aventis U.S. LLC. Diaβeta® (glyburide) Tablets USP. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017532s030lbl.pdf. [Accessed 5 December 2011].
98. Takeda Pharmaceuticals America. Actos (pioglitazone hydrochloride) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf. [Accessed 5 December 2011].
99. Bidstrup TB, Bjornsdottir I, Sidelmann UG, Thomsen MS, Hansen KT. **CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide.** *Br J Clin Pharmacol* 2003; **56**:305–314.
100. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. **Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide.** *Diabetologia* 2003; **46**:347–351.
101. Weaver ML, Orwig BA, Rodriguez LC, Graham ED, Chin JA, Shapiro MJ, *et al*. **Pharmacokinetics and metabolism of nateglinide in humans.** *Drug Metab Dispos* 2001; **29**:415–421.
102. Baldwin SJ, Clarke SE, Chenery RJ. **Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone.** *Br J Clin Pharmacol* 1999; **48**:424–432.
103. Oette M, Kurowski M, Feldt T, Kroidl A, Sagir A, Vogt C, *et al*. **Impact of rosiglitazone treatment on the bioavailability of antiretroviral compounds in HIV-positive patients.** *J Antimicrob Chemother* 2005; **56**:416–419.
104. Pentikainen PJ, Neuvonen PJ, Penttila A. **Pharmacokinetics of metformin after intravenous and oral administration to man.** *Eur J Clin Pharmacol* 1979; **16**:195–202.
105. Gupta SK. **Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system.** *AIDS Patient Care STDS* 2008; **22**:99–103.
106. Bige N, Lanternier F, Viard JP, Kamgang P, Daugas E, Elie C, *et al*. **Presentation of HIV-associated nephropathy and outcome in HAART-treated patients**. *Nephrol Dial Transplant* 2012; **27**:1114–1121.
107. Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivanis P. **Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV infection.** *J Ren Care* 2011; **37**:25–29.
108. Bayer HealthCare Pharmaceuticals. PRECOSE(R) (acarbose) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020482s024lbl.pdf. [Accessed 5 December 2011].
109. Pharmacia & Upjohn Company. Glyset(R) (miglitol) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020682s008lbl.pdf. [Accessed 5 December 2011].
110. Bristol-Myers Squibb Company. ONGLYZA(R) (Saxagliptin) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022350s007lbl.pdf. [Accessed 5 December 2011].
111. Boehringer Ingelheim International. Tradjenta™ (linagliptin) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201280lbl.pdf. [Accessed 5 December 2011].
112. Merck Sharp & Dohme. JANUVIA® (sitagliptin) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021995s017lbl.pdf. [Accessed 5 December 2011].
113. Berry SJ, Coffey DS, Walsh PC, Ewing LL. **The development of human benign prostatic hyperplasia with age.** *J Urol* 1984; **132**:474–479.
114. Sanofi-Aventis U.S. LLC. UROXATRAL® (alfuzosin HCl) extended-release tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021287s016lbl.pdf. [Accessed 17 December 2011].

115. Boehringer Ingelheim Pharmaceuticals. Flomax® (tamsulosin hydrochloride) Capsules. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020579s027lbl.pdf. [Accessed 17 December 2011].
116. Pfizer. VIAGRA® (Sildenafil citrate) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020895s036lbl.pdf. [Accessed 17 December 2011].
117. Eli Lilly and Company. CIALIS (tadalafil) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021368s20s21lbl.pdf. [Accessed 17 December 2011].
118. Bayer HealthCare Pharmaceuticals Inc. LEVITRA (vardenafil hydrochloride) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021400s013lbl.pdf. [accessed 17 December 2011].
119. Lallemand F, Salhi Y, Linard F, Giami A, Rozenbaum W. **Sexual dysfunction in 156 ambulatory HIV-infected men receiving highly active antiretroviral therapy combinations with and without protease inhibitors.** *J Acquir Immune Defic Syndr* 2002; **30**:187–190.
120. Asboe D, Catalan J, Mandalia S, Dedes N, Florence E, Schrooten W, *et al*. **Sexual dysfunction in HIV-positive men is multifactorial: a study of prevalence and associated factors.** *AIDS Care* 2007; **19**:955–965.
121. Nkuize M, De Wit S, Muls V, Arvanitakis M, Buset M. **Upper gastrointestinal endoscopic findings in the era of highly active antiretroviral therapy.** *HIV Med* 2010; **11**:412–417.
122. Welage LS, Carver PL, Revankar S, Pierson C, Kauffman CA. **Alterations in gastric acidity in patients infected with human immunodeficiency virus.** *Clin Infect Dis* 1995; **21**:1431–1438.
123. Wang X, Boffito M, Zhang J, Chung E, Zhu L, Wu Y, *et al*. **Effects of the H2-receptor antagonist famotidine on the pharmacokinetics of atazanavir-ritonavir with or without tenofovir in HIV-infected patients.** *AIDS Patient Care STDS* 2011; **25**:509–515.
124. Zhu L, Persson A, Mahnke L, Eley T, Li T, Xu X, *et al*. **Effect of low-dose omeprazole (20 mg daily) on the pharmacokinetics of multiple-dose atazanavir with ritonavir in healthy subjects.** *J Clin Pharmacol* 2011; **51**:368–377.
125. Fang AF, Damle BD, LaBadie RR, Crownover PH, Hewlett D Jr, Glue PW. **Significant decrease in nelfinavir systemic exposure after omeprazole coadministration in healthy subjects.** *Pharmacotherapy* 2008; **28**:42–50.
126. Tibotec Pharmaceuticals. EDURANT (rilpivirine) [Tablets]. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdf. [Accessed 6 December 2011].
127. Owe-Larsson B, Sall L, Salamon E, Allgulander C. **HIV infection and psychiatric illness.** *Afr J Psychiatry (Johannesbg)* 2009; **12**:115–128.
128. Maj M, Janssen R, Starace F, Zaudig M, Satz P, Sughondhabirom B, *et al*. **WHO Neuropsychiatric AIDS study, cross-sectional phase I. Study design and psychiatric findings.** *Arch Gen Psychiatry* 1994; **51**:39–49.
129. Lyketsos CG, Federman EB. **Psychiatric disorders and HIV infection: impact on one another.** *Epidemiol Rev* 1995; **17**:152–164.
130. Dube B, Benton T, Cruess DG, Evans DL. **Neuropsychiatric manifestations of HIV infection and AIDS.** *J Psychiatry Neurosci* 2005; **30**:237–246.
131. Atkinson JH Jr, Grant I, Kennedy CJ, Richman DD, Spector SA, McCutchan JA. **Prevalence of psychiatric disorders among men infected with human immunodeficiency virus. A controlled study.** *Arch Gen Psychiatry* 1988; **45**:859–864.
132. Bloch F, Thibaud M, Dugue B, Breque C, Rigaud AS, Kemoun G. **Psychotropic drugs and falls in the elderly people: updated literature review and meta-analysis.** *J Aging Health* 2011; **23**:329–346.
133. Villes V, Spire B, Lewden C, Perronne C, Besnier JM, Garre M, *et al*. **The effect of depressive symptoms at ART initiation on HIV clinical progression and mortality: implications in clinical practice.** *Antivir Ther* 2007; **12**:1067–1074.
134. Caballero J, Nahata MC. **Use of selective serotonin-reuptake inhibitors in the treatment of depression in adults with HIV.** *Ann Pharmacother* 2005; **39**:141–145.
135. van der Lee MJ, Blenke AA, Rongen GA, Verwey-van Wissen CP, Koopmans PP, Pharo C, *et al*. **Interaction study of the combined use of paroxetine and fosamprenavir-ritonavir in healthy subjects.** *Antimicrob Agents Chemother* 2007; **51**:4098–4104.
136. GlaxoSmithKline. PAXIL® (paroxetine hydrochloride) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020031s058s066,020710s022s030lbl.pdf. [Accessed 6 December 2011].
137. DeSilva KE, Le Flore DB, Marston BJ, Rimland D. **Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine.** *AIDS* 2001; **15**:1281–1285.
138. Eli Lilly and Company. PROZAC (fluoxetine hydrochloride) Pulvules for oral use. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018936s096,021235s018lbl.pdf. [Accessed 8 December 2011].
139. de Maat MM, Huitema AD, Mulder JW, Meenhorst PL, van Gorp EC, Mairuhu AT, *et al*. **Drug interaction of fluvoxamine and fluoxetine with nevirapine in HIV-1-infected individuals.** *Clin Drug Investig* 2003; **23**:629–637.
140. Forest Pharmaceuticals. VIIBRYD (vilazodone HCl) Tablets for oral administration. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s001lbl.pdf. [Accessed 9 December 2011].
141. Eli Lilly and Company. Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules for Oral Use. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021427s039lbl.pdf. [Accessed 8 December 2011].
142. Wyeth Pharmaceuticals Inc. Effexor® (venlafaxine hydrochloride) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020151s056s057lbl.pdf. [Accessed 8 December 2011].
143. Wyeth Pharmaceuticals Inc. PRISTIQ® (desvenlafaxine) Extended-Release Tablets, oral. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021992s022lbl.pdf. [Accessed 9 December 2011].
144. Levin GM, Nelson LA, DeVane CL, Preston SL, Eisele G, Carson SW. **A pharmacokinetic drug-drug interaction study of venlafaxine and indinavir.** *Psychopharmacol Bull* 2001; **35**:62–71.
145. Schering-Plough Corporation. REMERON® (mirtazapine) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020415s023s024.pdf. [Accessed 8 December 2011].
146. Fox CB, Treadway AK, Blaszczyk AT, Sleeper RB. **Megestrol acetate and mirtazapine for the treatment of unplanned weight loss in the elderly.** *Pharmacotherapy* 2009; **29**:383–397.
147. Greenblatt DJ, von Moltke LL, Harmatz JS, Fogelman SM, Chen G, Graf JA, *et al*. **Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone.** *J Clin Pharmacol* 2003; **43**:414–422.
148. Hoffmann-La Roche Inc. INVIRASE© (saquinavir mesylate) Capsules and Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020628s033,021785s010lbl.pdf. [Accessed 8 December 2011].
149. ViiV Healthcare. SELZENTRY (maraviroc) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022128s007lbl.pdf. [Accessed 8 December 2011].
150. Hogeland GW, Swindells S, McNabb JC, Kashuba AD, Yee GC, Lindley CM. **Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects.** *Clin Pharmacol Ther* 2007; **81**:69–75.
151. Lavrut T, Ferrand S, Durant J, Lavignon M, Sabo JP, Dellamonica P, Garraffo R. **Effect of tipranavir/ritonavir treatment on the steady-state pharmacokinetics of bupropion in healthy volunteers** [abstract P4.3/03]. *11th European AIDS Conference*; 24–27 October 2007; Madrid, Spain.
152. Robertson SM, Maldarelli F, Natarajan V, Formentini E, Alfaro RM, Penzak SR. **Efavirenz induces CYP2B6-mediated hydroxylation of bupropion in healthy subjects.** *J Acquir Immune Defic Syndr* 2008; **49**:513–519.

153. Park-Wyllie LY, Antoniou T. **Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series.** *AIDS* 2003; **17**:638–640.
154. Aung GL, O'Brien JG, Tien PG, Kawamoto LS. **Increased aripiprazole concentrations in an HIV-positive male concurrently taking duloxetine, darunavir, and ritonavir**. *Ann Pharmacother* 2010; **44**:1850–1854.
155. Bristol-Myers Squibb Company. ABILIFY® (aripiprazole) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021436s032,021866s019,021713s024,021729s017lbl.pdf. [Accessed 9 December 2011].
156. Penzak SR, Hon YY, Lawhorn WD, Shirley KL, Spratlin V, Jann MW. **Influence of ritonavir on olanzapine pharmacokinetics in healthy volunteers.** *J Clin Psychopharmacol* 2002; **22**:366–370.
157. AstraZeneca Pharmaceuticals. SEROQUEL® (quetiapine fumarate) Tablets. Prescribing information [online]. http://www. accessdata.fda.gov/drugsatfda_docs/label/2011/020639s049s054lbl.pdf. [Accessed 9 December 2011].
158. Jover F, Cuadrado JM, Andreu L, Merino J. **Reversible coma caused by risperidone-ritonavir interaction.** *Clin Neuropharmacol* 2002; **25**:251–253.
159. Pfizer. GEODON (ziprasidone HCl) capsules. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020825s038,020919s025,021483s005lbl.pdf. [Accessed 9 December 2011].
160. Novartis Pharmaceuticals Corporation. CLOZARIL® (clozapine) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019758s 063lbl.pdf. [Accessed 9 December 2011].
161. Novartis Pharmaceuticals Corporation. FANAPT® (iloperidone) tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022192s005s006lbl.pdf. [Accessed 9 December 2011].
162. Ortho-McNeil-Janssen Pharmaceuticals. INVEGA® (paliperidone) Extended-Release Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021999s020s024lbl.pdf. [Accessed 9 December 2011].
163. Teva Pharmaceuticals. ORAP® (pimozide) Tablets. Prescribing information [online]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017473s046lbl.pdf. [Accessed 9 December 2011].
164. Volavka J, Convit A, Czobor P, Douyon R, O'Donnell J, Ventura F. **HIV seroprevalence and risk behaviors in psychiatric inpatients.** *Psychiatry Res* 1991; **39**:109–114.
165. Susser E, Valencia E, Conover S. **Prevalence of HIV infection among psychiatric patients in a New York City men's shelter.** *Am J Public Health* 1993; **83**:568–570.
166. Cournos F, Guido JR, Coomaraswamy S, Meyer-Bahlburg H, Sugden R, Horwath E. **Sexual activity and risk of HIV infection among patients with schizophrenia.** *Am J Psychiatry* 1994; **151**:228–232.
167. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, *et al*. **Risk of death in elderly users of conventional vs. atypical antipsychotic medications.** *N Engl J Med* 2005; **353**:2335–2341.
168. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, *et al*. **Effectiveness of antipsychotic drugs in patients with chronic schizophrenia.** *N Engl J Med* 2005; **353**:1209–1223.
169. Periard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ, *et al*. **Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study.** *Circulation* 1999; **100**:700–705.
170. Brown TT, Qaqish RB. **Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review.** *AIDS* 2006; **20**:2165–2174.
171. Triant VA, Brown TT, Lee H, Grinspoon SK. **Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system.** *J Clin Endocrinol Metab* 2008; **93**:3499–3504.
172. Stellbrink HJ, Orkin C, Arribas JR, Compston J, Gerstoft J, Van Wijngaerden E, *et al*. **Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study.** *Clin Infect Dis* 2010; **51**:963–972.
173. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, *et al*. **Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202.** *J Infect Dis* 2011; **203**:1791–1801.
174. Rozenberg S, Lanoy E, Bentata M, Viard JP, Valantin MA, Missy P, *et al*. **Effect of alendronate on HIV-associated osteoporosis: a randomized, double-blind, placebo-controlled, 96-week trial (ANRS 120)**. *AIDS Res Hum Retroviruses* 2012 [Epub ahead of print].