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Epidemiology of HIV and response to antiretroviral therapy in the middle aged and elderly

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Abstract

HIV is increasing in prevalence in the middle aged and older population owing to both increased longevity, and new infections in these populations. Highly active antiretrorival therapy (HAART) therapy may be less effective at restoring immune function in older patients compared with younger patients. There are significant toxicities associated with HAART therapy that, combined with decreased renal and liver function in older patients, may be more problematic in older HIV-infected patients. Comorbid disease is becoming an increasing problem with coadministration of multiple drugs and significant drug–drug interactions. Psychosocial issues in the older patient are often different than those in younger HIV-infected patients and providers should try to address these issues early. Finally, future research should work to identify the ideal timing and type of HAART regimens for older HIV-infected individuals.

Keywords

age; aging; antiretroviral therapy; elderly; HIV; mortality

The percentage of all HIV cases in patients aged 50 years or over has increased to over 17% in the most recent US CDC statistics [1]. This increase in prevalence of HIV in middle aged and older people will continue with the aging of the HIV-infected population and new infections in older patients. In fact, the US Senate Special Committee on Aging recently predicted that by 2015, 50% of nationally prevalent HIV/AIDS cases will be in this older age group [2]. With the advent of highly active antiretroviral therapy (HAART), the prognosis for older patients has changed. Older patients are more likely to achieve virologic suppression than younger patients, but achieve less immune recovery with advancing age [3–16]. There are numerous toxicities with HAART of virtually all organ systems. Reported toxicities include, but are not limited to, diabetes, hepatotoxicity, renal insufficiency, dyslipidemia, pancreatitis, neuropathy and lactic acidosis [17–45]. Comorbidities are more common in older patients and their comanagement can complicate HIV treatment. Given the decreased immune recovery with HAART, early therapy may be warranted; however, the increased toxicity may not be worth the immunologic benefit. Future work will need to identify the ideal timing and type of HAART regimens for older HIV-infected individuals.

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Epidemiology

The epidemiology of the HIV-infected population is changing with more middle aged and older patients affected [46–54]. The CDC identified patients aged 50 years or over as a separate age group, because this age group was so much older compared with the mean age of HIV patients early in the HIV epidemic [55]. HIV patients are aging because of the increased survival owing to HAART, and there are a mounting number of new HIV infections in older patients due to high-risk exposures [56]. The number of HIV-infected persons over 65 years of age has grown tenfold in the past 10 years [48].

Consistent with the demographic shift seen in younger patients, increasing numbers of women and non-Caucasian older patients are currently affected by the HIV epidemic. Of the AIDS cases among men 60 years or over in 1999, 70% were in minorities. Among women with AIDS over 60 years, 60% were black [56]. This is particularly concerning given that the minority group of older HIV-infected patients are more likely to be economically disadvantaged and more likely to suffer from lower levels of physical functioning and emotional support than younger HIV patients [57].

Older patients are often diagnosed at a worse stage of HIV than younger patients [58–61]. This is most likely because healthcare providers are less likely to ask older patients about high-risk behaviors, or even suspect HIV in older patients [48,60,62]. In addition, even though older patients may be engaging in high-risk sexual activity [63,64], they may be less likely to admit to these behaviors [46]. Older patients may not recognize the risk of unprotected sexual intercourse or of having multiple partners because they were not raised in the era of safe sex. A study of 181 women with a mean age of 58.0 years from rural South Carolina, nearly half of whom were married, found that over two thirds had at least one sex partner in the past 5 years, and of these, nearly 60% reported at least one sexual risk behavior [64]. In this study, high-risk behavior was associated with less education, lower condom use control by the woman, and less comfort communicating with partners about sex. Older Americans, particularly older African–American women, appear to be at increased risk for HIV infection, suggesting a need for HIV-prevention efforts that target older individuals.

Clinical response to HAART

Highly active antiretroviral therapy clearly reduces morbidity and mortality associated with HIV. It decreases circulating HIV and, in general, improves CD4 lymphopenia. The clinical, immunologic and virologic benefit in older patients treated with HAART has been different than in younger patients (Table 1).

There is controversy over the rates of virologic suppression and CD4 response in older versus younger patients on HAART. Some authors have demonstrated increased virologic suppression in older compared with younger patients [65–69], another demonstrated better virologic suppression in younger patients [70], and several have demonstrated no difference in virologic suppression between older and younger patients [71–73]. Similarly, some studies have demonstrated a smaller CD4 reconstitution in older patients compared with younger patients treated with HAART [68,69,71,74–77] while others have not noted a significant difference in CD4 response in older versus younger patients [67,72,73,78] on HAART.

The most impressive study to examine the impact of HIV and aging evaluated nearly 50,000 HIV-infected Europeans who were antiretroviral-naive and compared patients response by decade of age. Compared with those aged 30–39 years at HAART initiation, the probability of virologic response was higher in those aged 50–54 (1.24), 55–59 (1.24) and those 60 years or over (1.18). However, those aged 60 years or over were 7% less likely to experience an

immunologic response compared with those aged 30–39 years. One significant limitation is that this study did not examine differences in response by HAART treatment class.

Two studies have examined the impact of regimen type on clinical outcomes by age. Patterson *et al.* demonstrated that immune reconstitution and viral suppression did not vary by treatment regimen when stratified by age. However, Greenbaum *et al.* found a significantly decreased time to virologic suppression in older patients on non-nucleoside reverse transcriptase inhibitors (NNRTIs) compared with younger patients on NNRTIs or protease inhibitors (PIs). In her study, there was no difference in time to virologic suppression in older patients on NNRTIs versus PIs [79]. Of note, both studies had relatively small sample sizes. Future studies will need to be adequately powered to identify the most appropriate antiretroviral therapy treatment type in older patients.

Studies evaluating HIV progression in older patients have also produced conflicting results. Several recent studies however have found that despite higher rates of virologic suppression, older patients have an increased risk of new opportunistic infections (OIs) compared with younger patients [68,80,81], although a recent study from Baltimore demonstrated fewer OIs in older HAART-naive patients compared with younger patients after starting HAART [79]. As expected, mortality rates are generally greater in older patients compared with younger patients [49,79,82]. Although in patients treated with HAART, the cause of death is generally non-HIV related in American and European cohorts [83–87].

In summary, there are conflicting data regarding clinical outcomes in older patients treated with HAART. The heterogeneity of the above mentioned studies – some are cross-sectional, others are longitudinal and many use different outcomes or cut-offs for virologic suppression – probably contribute to this issue. Several small trials have attempted to, but no large trial has evaluated, the effect of any one HAART regimen or even class of HAART in regard to outcomes in older versus younger HIV-infected patients. Therefore, current conclusions regarding HAART therapies in older patients are limited. Larger controlled trials involving older patients are necessary to evaluate which antiretroviral therapies might be most effective in this population. Until then, current guidelines for HAART regimens should be applied to HIV-infected older patients. Immunologic, virologic and clinical responses should be monitored carefully after HAART has commenced.

HAART toxicity

Most studies of antiretroviral metabolism have excluded patients of advanced age with comorbid disease; therefore, there is relatively little data on the toxicities of antiretrovirals in elderly HIV patients. The toxicities of antiretroviral therapy can be the limiting factor in the effective management of HIV with HAART therapy as they can cause increased morbidity and reduced quality of life. Side effects can also result in decreased adherence [88,89]. Adverse effects of HAART include disorders of lipid and glucose metabolism, hepatotoxicity, pancreatitis, peripheral neuropathy, liposdystrophy (including peripheral fat loss and/or central fat accumulation), osteopenia, osteoporosis, avascular bone necrosis and lactic acidosis [17–45]. While the pathophysiologic mechanisms of these toxicities include mitochondrial abnormalities and metabolic and endocrinologic disorders, in many cases, the mechanism appears to be multifactorial.

With increasing age, there is a normal reduction in creatinine clearance and this reduction in renal function can affect metabolism of renally excreted medications. In addition, the methods used for estimating renal function, which only use serum creatinine, may miss older patients with reduced renal function owing to their lower relative muscle mass [90]. Advanced HIV disease is also associated with reduced muscle mass as well, making estimation of renal function even more difficult [91]. NRTIs are eliminated through both tubular secretion and

glomerular filtration. Therefore, with the exception of abacavir, NRTIs need to be dose adjusted in patients with reduced renal function. NNRTIs and PIs generally do not require any dosage adjustment with renal insufficiency. Tenofovir is nephrotoxic and indinavir is associated with nephrolithiasis [34–39,44], and these drugs may be more dangerous in the elderly, those with comorbidities such as hypertension or diabetes or when used in combination with other antiretrovirals [45].

With normal aging, there is a decrease in liver size and blood flow. In addition, HIV patients are commonly infected with hepatitis viruses and may have prior histories of heavy drug or alcohol use. HIV patients with hepatic insufficiency deserve special attention when certain antiretroviral drugs are used. Most PIs and NNRTIs can exacerbate hepatic insufficiency in those with pre-existing liver disease [92–95]. In addition, hepatotoxicity with multidrug HAART and potential interactions with other medications including antituberculous therapy and lipid-lowering agents, make screening of liver function of paramount importance in HIV patients [96].

Little data exists on dosing of these drugs in older patients with impaired hepatic clearance. Interactions between different antiretroviral agents are common and have been used to improve activity of some HAART regimens, such as the use of ritonavir as a booster for other PIs. There are few data on the pharmaco-kinetics of these drugs in the extremes of age, and older patients may be more likely to have drug–drug interactions.

Pharmacologic interactions between antiretroviral agents and other drugs used in the elderly are common and contraindicated drug combinations should be avoided (Table 2). Many common drugs in older patients also interact with antiretrovirals, although are not necessarily contraindicated. Caution should be exerted with concomitant use of PIs and erectile dysfunctional (ED) drugs such as sildenafil owing to the potential for PIs to increase the levels of the sildenafil. Patients should start on low doses of the ED drugs and be warned of the potential side-effects. Providers should screen all potential drug–drug interactions before prescribing new medications to HIV-infected patients.

There is a need for information about treatment tolerability, drug–drug interactions, short- and long-term toxicity, and interactions with other non-HIV medications in older adults. Most randomized, controlled trials evaluating new antiretroviral drugs or chemoprophylaxis of HIV-related complications excluded either patients with advanced age and/or comorbidities. Few studies have offered subanalysis comparing outcomes of older patients with younger ones. Older age is associated with a high rate of adverse events from pharmacologic agents, therefore, careful monitoring is required with the use of antiretroviral and opportunistic illness prophylaxis medications in older HIV-infected patients [97,98]. Finally, it will also be important to identify the long-term consequences of HAART therapy as the HIV-infected population ages.

Comorbidities

With appropriate antiretroviral treatment, HIV has evolved into a chronic disease that may accelerate the risk of many comorbidities of aging so that these conditions develop at an earlier age than in HIV-seronegative patients [99,100]. Furthermore, with normal aging there is weight loss, decreased glomerular filtration rate, memory loss, immuno-senescence, increased pain, and loss of bone and muscle mass. In addition to chronic HIV infection, older patients are also suffering from other medical comorbidities that they previously did not live long enough to endure, including bacterial and viral infections, cancer and vascular disease.

Shah and colleagues evaluated 165 HIV-infected patients older than 55 years of age in New York City, NY, USA. They identified a mean of 2.4 comorbidities and 2.7 non-HIV

medications per patient [101]. In this study, the most common comorbidities were hypertension (41%), chronic obstructive pulmonary disease (29%) and diabetes mellitus (22%). Of note, the most common medications were β-agonists and calcium-channel blockers, although antihypertensives as a class were the most commonly used medication.

Age independently predicts risk for cardiovascular disease. With advancing age there is an accumulation of atherosclerosis, which predicts the likelihood of suffering a cardiovascular event [102]. Previous data has indicated an increased risk of cardiovascular and cerebrovascular events in those infected with HIV. However, controversy exists on the association of these events with HAART. Several have found an association between HAART and cardiovascular events [31–33], while others have not found this association [103,104]. A large study identified a possible increased risk of myocardial infarction with use of abacavir [105], although other studies have not been able to confirm this data as of yet. Recent data from HAART-naive patients demonstrated increased rates of hypertension 1 year after starting antiretroviral therapy [106]. Clearly, primary prevention with appropriate screening for cardiovascular risk factors including hypertension, tobacco abuse, hyperlipidemia and diabetes or impaired glucose tolerance is essential by HIV providers.

Older HIV-infected patients are more likely to have neurocognitive problems including depression and dementia than age-matched HIV-negative controls [107–110]. Dementia in HIV-infected older adults can be from a number of different diseases including Alzheimer's, multi-infarct dementia, HIV-associated mild neurocognitive disorder or AIDS-related dementia. According to the American Academy of Neurology, HIV-associated dementia (HAD) is combination of limitations in cognitive abilities plus abnormalities in motor function or changes in emotional or behavioral functioning [111]. Large, longitudinal studies are needed to identify if there are age-related differences in the prevalence and severity of cognitive dysfunction in HIV-infected older adults.

A study of HIV-infected veterans demonstrated a greater prevalence of depressive symptoms in HIV-infected veterans than HIV-negative age-matched counterparts. Although depressive symptoms decreased with age in the study, the difference in prevalence between the HIV-negative and -positive groups increased with age. In addition, older HIV-infected veterans were more likely to have a diagnosis of alcohol abuse or dependence than HIV-negative age-matched controls. In addition, current drug use, drug abuse or dependence was more common among HIV-positive veterans than HIV-negative counterparts [109]. Finally, this study demonstrated an increase in memory problems associated with advancing age in both HIV-infected and HIV-seronegative study subjects. Practitioners who are unfamiliar with management of these conditions need to seek assistance in the treatment of these drug and alcohol issues in this population. Future research into the etiology, prevalence and treatments of neurocognitive disorders will be needed to improve care of these older HIV-infected patients.

Older HIV-infected women enter menopause at an earlier age than HIV-seronegative controls (who enter menopause at a median of 51 years) [112–115]. In fact, a recent study demonstrated that the median age of menopause in HIV-infected women was 46 years, with an interquartile range of 39–49 years [112]. A study by Clark *et al.* found that HIV-infected women often experience several symptoms associated with menopause, although relatively few were receiving hormone-replacement therapy (HRT) [113]. Interestingly, in a cohort in New Orleans, LA, USA, Clark found that use of HRT in older women decreased overall mortality [116]. This would suggest that further studies evaluating the impact of HRT on older HIV-infected women are warranted.

Frailty is typically defined by decreased physical reserves and is known to increase risk sof morbidity and mortality. Fried and colleagues found a low prevalence of frailty among HIV-

infected individuals in the United States Multicenter AIDS Cohort Study (MACS) [117], although they did find that frailty occurred earlier in HIV-infected patients compared with seronegative controls. Others have shown that middle-aged, HIV-infected men on HAART have reductions in exercise capacity, functional performance [118], physical activity and grip strength. Since frailty is associated with poorer health outcomes than a more robust physical stature [118,119], clinicians should be aware of their patients functional as well as physical status.

The management of comorbidities complicates overall management of the older patient [120, 121] and the HIV-infected older patient. Previous studies evaluating comorbidities in HIV have been limited by relatively few minorities and older people [122,123]. It is unknown if HIV-infected older patients on HAART will have higher rates of comorbidities than HIV-infected age-matched controls not on HAART. HAART therapy may have a synergistic effect with HIV to increase the incidence of comorbidities and may interact with comorbidities and their treatment. Alternatively, HAART may improve immune function and may reduce the development of certain comorbidities. Understanding the prevalence and incidence of these comorbidities and the effect of comorbidities on HIV disease progression is critical in the management of older HIV-infected individuals.

General routine medical care

In addition to comanagement of HIV and other comorbidities, HIV-infected older patients require routine age-related health maintenance. We must learn to prioritize and coordinate screening and treatment for important comorbid conditions while maintaining excellence in the care of HIV infection. Combination antiretroviral therapy has revolutionized the care of HIV infection. Randomized trial data now support continuous antiretroviral management of HIV infection, even among those with comorbid disease [124]. Earlier data have demonstrated that many ‘non-AIDS’ conditions improve with effective antiretroviral therapy [125,126]. It is clear that getting patients on an effective regimen and insuring that they are acceptably adherent remains paramount. However, there still remain patients who will require careful attention to alcohol and drug use and depressive symptoms before they can achieve acceptable adherence.

Once adherent to an effective HAART regimen, patients will have substantial comorbid medical disease that will require targeted screening and treatment. The approach to these conditions must be guided by the costs and benefits in our population of patients. Screening and treatment that requires a life expectancy beyond 10 years, for example, colon cancer screening, should be undertaken only among those deemed likely to live that long. Otherwise we will be exposing our patients to immediate potential harms (the risk of perforation from colonoscopy and the pain and discomfort of the preparation and the procedure) without the likelihood of future benefit [83]. We will also need to think carefully about what conditions our patients are at particularly high risk from (e.g., HCV, alcohol and tobacco use) and target these accordingly. Finally, as more data become available, we need to consider how mechanisms of common comorbid diseases may differ among those with HIV infection and the implications for management these mechanisms imply.

Current recommendations of the American Cancer Society and the United States Preventive Task Force include colorectal cancer screening starting at 50 years of age for all persons at average risk for colorectal cancer [127,128]. A study in the Veterans Administration demonstrated that HIV-infected patients over 50 years of age were significantly less likely than age-matched controls to be up to date with one colorectal screening test according to current guidelines (49 vs 66%, respectively) [129]. This has been confirmed in several other studies in HIV populations [101,130].

A study in an urban cohort of HIV patients demonstrated that 80% of older HIV-infected women were referred for Papanicoloau smears in the year prior to their last recorded visit, and 58% actually received the examination. Similar results were seen for mammography where 56% of older HIV-infected women were referred and 32% actually received the examination [130]. While the rates of cervical cancer screening and mammography in this study are consistent with several national studies in eligible HIV-negative women [131,132], the high risk of cervical cancer in HIV-infected women and increasing proportion of HIV patients with non-AIDS malignancies suggests that appropriate increased vigilance to recommended cancer screening protocols should be maintained by healthcare providers, so long as the patient's life expectancy is consistent with these recommendations.

Psychosocial issues in older HIV patients

Psychosocial issues in the older patient with HIV are being recognized as increasingly important in overall medical management. As in HIV-infected children, disclosure has to be handled carefully in older patients. In fact, recent research has shown that many older patients had their confidentiality involuntarily violated [133]. Many older patients with HIV fear becoming isolated from family members and friends owing to disapproval of HIV risk behaviors. There are an increasing number of support groups for older Americans with HIV, including the National Association on HIV Over Fifty (NAHOF) and the HIV Wisdom for Older Women. Many patients report that age-specific support groups have been helpful [134]. Finally, older patients are often more concerned about end-of-life issues and adequately addressing these while the patient is healthy can help ensure that the patients wishes are fulfilled when end-of-life issues arise. In summary, an important focus of HIV care for the older patient should include a social work consult and referral for age-appropriate support groups if possible.

Conclusion & future perspective

The prevalence of middle aged and elderly people with HIV will continue to increase over the next decade. Until recently, this population has been relatively ignored and controlled trials on the therapeutic and clinical outcomes of older HIV-infected patients are needed. While HAART has been effective in reducing morbidity and mortality, these clinical improvements may be tempered by the development of resistant HIV and toxicities from antiretroviral therapy, particularly in older patients. Furthermore, with the aging population, the development and management of comorbidities will make HIV treatment more complex. Newer classes of antiretroviral drugs that have recently been released or that are in development may help reduce issues of resistance and the new coformulations of antiretrovirals may help increase adherence through once-daily treatment options. The toxicity from HAART is significant and it is unclear if these toxicities are greater in older patients. Therefore, research to evaluate the impact of age on clinical outcomes and adverse drug events in HIV-infected patients overall and by antiretroviral therapy treatment class is needed and likely to improve our understanding of the role of age in clinical care of HIV infection.

Executive summary

- The prevalence of HIV in patients over 50 years of age is increasing owing to increased longevity as well as new primary infections in older patients.
- Older patients treated with highly active antiretroviral therapy (HAART) have superior virologic response compared with younger patients, but decreased immunologic response.
- There are numerous HAART-associated toxicities that may be greater in older compared to younger patients.

- Comorbidities in HIV-infected patients appear to be more numerous and occur at an earlier age than in HIV-seronegative patients. Comanagement of comorbidities in HIV-infected patients requires close discussion between providers, patients and other caregivers to optimally manage pill burden and reduce drug–drug interactions.
- Psychosocial issues in older HIV-infected patients are numerous; however, disclosure is often the most difficult. Providers should work to help patients disclose their illness to families in the most supportive environment possible.
- Future research is needed to evaluate the toxicities and effectiveness of HAART in older patients, in order to develop accurate treatment recommendations for older HIV patients.

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Table 1

Recent studies with more than 150 patients evaluating immunologic and virologic responses to highly active antiretroviral therapy stratifying by age.

Author	Study design	Follow-up	n	Age group	CD4 increases	Viral load after treatment	Ref.
Viard, (2001)	Cohort	24–36 months	1956 (total)	<33 ≥45	Time to increase in CD4 by more than 200 cells/mm^3: Relative hazard 1.00 0.8 (0.7, 0.9)	NR	[74]
Knobel, (2001)	Cohort	24 months	671 28	≤40 ≥60	Mean increase (SD): 228 (145) 196 (100)	≤50: 51% 67%	[69]
Yamashita, (2001)	Cohort	3–33 months	397	<45 ≥45	Decreased 3-month CD4 response in those <45 years of age, no effect of age on 6-month CD4	<400: no difference by age group	[72]
Tumbarello, (2003)	Case– control		116 58	20–35 ≥50	Increase to CD4 > 200: 79.0 69.0 (p = ns)	≤50: 72% 79%; p = ns	[73]
Grabar, (2004)	Cohort	Median 32 months	2614 401	<50 ≥50	Mean increase in CD4: 17.3 cells/month 14.1 cells/month	≤500: 70.6% 76.6%	[68]
Tumbarello, (2004)	Case– Control	6 months–6 years	476 120	20–35 >50	Increase in CD4 to >200: 79.0 73.0 (p=ns)	<50: 75% 82%	[67]
COHERE, (2008)	Cohort		2593 1656 1613	50–54 55–59 ≥60	Time to increase to 100 cells/mm: greatest time in patients >60 years	Time to viral load <400: less time in patients <60 years >	[82]
Patterson, (2007)	Cohort	6 months	63 183	<50 ≥50		<400: 67% 75%	[136]
Silverberg, (2007)	Cohort	1 year	2259 1834 997	18–39 40–49 >50	Adjusted mean increase in CD4 at 1 year: 142 128 113	AHR of <500: 1.0 0.97 (0.89; 1.06) 1.07(0.95; 1.2)	[138]
Cuzin, (2007)	Cohort	6 mos	540 99	<50 ≥50	Median increase at 6 months: 100 104	NR	[137]
Bosch, (2007)	ALLRT Cohort	144 weeks	1083			Per 10 years age, ARR 1.05 (1.01–1.09) of viral load <50 at 144 weeks	[135]

ALLRT: AIDS longitudinal randomized trials; AHR: Adjusted hazard ratio; ARR: Adjusted rate ratio; NR: Not reported.

Table 2

Common drug–drug interactions of antiretrovirals for compounds often used in the elderly.

	Drug category									
Anti-retroviral	**Anti-histamines**	**Anti-microbials**	**Cardiovascular agents**	**Chemotherapy agents**	**GI drugs**	**Lipid-lowering agents**	**Neurologic drugs**	**Illicit drugs**	**Others**	**Herbals**
Atazanavir	Astemizole Terfenadine	Rifampin Rifapentene	Beperidil Ranolazine	Irinotecan	Proton- pump inhibitors	Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Darunavir	Astemizole Terfenadine	Rifampin Rifapentene	Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Fosamprenavir	Astemizole Terfenadine	Rifampin Rifapentene	Flecainide Propafenone Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Indinavir	Astemizole Terfenadine	Rifampin Rifapentene	Amiodarone Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Lopinavir/ritonavir	Astemizole Terfenadine	Rifampin Rifapentene	Amiodarone Flecainide Propafenone Quinidine Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)	Alfuzosin	St. John's Wort
Nelfinavir	Astemizole Terfenadine	Rifampin Rifapentene	Amiodarone Beperidil Quinidine Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Ritonavir	Astemizole Astemizole Terfenadine	Rifapentene Metronidazole	Amiodarone Beperidil Flecainide Propafenone Quinidine Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)	Alfuzosin	St. John's Wort
Saquinavir	Astemizole Terfenadine	Rifampin Rifabutin Rifapentene	Amiodarone Beperidil Flecainide Propafenone Quinidine Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Tipranavir	Astemizole Terfenadine	Rifampin Rifabutin Rifapentene	Amiodarone Beperidil Flecainide Propafenone Quinidine Ranolazine			Lovastatin Simvastatin	Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)	Alfuzosin	St. John's Wort
Delavirdine	Astemizole Terfenadine	Rifampin Rifabutin Rifapentene	Ranolazine		H_2-blockers Proton- pump inhibitors		Alprazolam, midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Efavirenz	Astemizole Terfenadine	Voriconazole					Midazolam, triazolam, ergot alkaloids and pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Nevirapine		Rifampin Rifapentene					Pimozide	γ-hydrobutyrate MDMA (ecstasy)		St. John's Wort
Maraviroc										St. John's Wort

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Antiretroviral drugs listed on the left should not be administered with drugs on the right.