Clinical Pharmacokinetics of Antiretroviral Drugs in Older Persons

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Abstract

Introduction—Combination antiretroviral therapy has enabled HIV infected persons to reach older ages in high numbers. Hepatic and renal changes that normally occur with advancing age occur earlier and with higher incidence in HIV-infected individuals. A limited number of prospective controlled studies have demonstrated small reductions (17% to 41%) in lopinavir, atazanavir, and lamivudine clearance in older versus younger adults. A much larger number of retrospective studies in adults (age range ~20 to 60 years), including all antiretroviral drugs, have evaluated age as a covariate for pharmacokinetics. Most studies did not detect substantial associations between drug exposures and age.

Areas Covered—This review summarizes antiretroviral drug pharmacokinetics in older persons. The authors review articles from PubMed (search terms: elderly, antiretroviral, pharmacokinetics) in addition to the bibliographies of those selected.

Expert Opinion—The evidence to date does not support major pharmacokinetic changes in adults between ~20 and 60 years of age. However, additional prospective, well-controlled studies are needed in more persons > 60 years, including those with frailty and comorbidities, with assessment of unbound drug clearance, and incorporation of adherence, pharmacogenetics, and concomitant medications. Until then, guidelines for drug-drug interactions and dosing in renal and hepatic impairment should be followed in older HIV infected individuals.

Keywords

antiretroviral therapy; clinical pharmacology; elderly; HIV; pharmacokinetics

1. Introduction

As a result of the effectiveness of antiretroviral therapy, HIV infected persons are reaching older ages in high numbers.[*1, 2] In the next several years, the average age for HIV infected persons will surpass 50 years, ushering in a new era of HIV management, heavily influenced by considerations for older persons.[3]

Medication use in older persons is complicated by end-organ dysfunction, slowed drug elimination, and polypharmacy of comorbidities with an elevated risk of drug-drug interactions, all contributing to unpredictable drug responses in older persons.[4] The onset of end-organ dysfunction and comorbidities in older HIV infected persons is earlier than in those without HIV infection, by approximately 10 years.[*5, *6] Thus, these general end-organ deficits and concerns are of particular importance among those aging with HIV infection. Prompted by these general concerns, the FDA has designated adults 65 or older as a unique patient population, signifying the need for informed drug use decisions in this population.[7] Understanding pharmacokinetic differences in older persons underlies the basis to make informed treatment decisions. When this information is not available, the following standard statement is required for the FDA-approved product label, "*Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.*" This standard statement (or similar wording) occupies all antiretroviral drug labels, because pharmacokinetic and pharmacodynamics information in older adults is lacking for nearly all antiretroviral drugs. Therefore, clinicians who treat older persons with antiretroviral therapy have little guidance in dose adjustment, drug interactions, or safe monitoring.

This review will discuss pharmacokinetic considerations for antiretroviral drugs in older patients and examine the published prospective and retrospective studies evaluating the association between older age and antiretroviral drug pharmacokinetics. The PubMed database was searched with the following terms: "elderly, HIV, antiretroviral, pharmacokinetics". Titles and abstracts were evaluated for pharmacokinetic studies in adults that included age in the analysis. Articles were selected if age was examined as a covariate in pharmacokinetic studies. Additionally, articles were selected from the bibliographies of these studies, and drug package inserts were evaluated for additional pharmacokinetic information in older patients.

2. Aging with HIV infection and antiretroviral drug pharmacokinetics

2.1 Epidemiology of HIV and aging

Antiretroviral therapy has enabled HIV infected people to live life spans that approach the general population.[8] Additionally, 10% to 20% of new HIV infections are in those over 50 years old.[2, 3] The Centers for Disease Control and Prevention have designated 50 years as "older" for HIV infected persons.[*9] The 50 years distinction differs from HIV-uninfected populations, where "older" is usually defined as 65 years, and the distinction does not appear to be based upon well-established physiological definitions.[*9, 10] At the end of 2009, approximately 40,300 HIV infected persons in the United States were 65 or older, and 155,700 were 55–64 demonstrating that further aging definitions will be needed in the near future.[3] Aging is also relevant for sub-Saharan Africa where 3 million persons with HIV-infection are 50 years or older.[11, 12] These numbers are expected to increase steadily in the ensuing years, as the age demographic continues to shift.[11, 13]

More important than chronological age is the presence of co-morbid conditions, and declines in physiological function with older age, including renal and hepatic function.[14] Multiple studies suggest that significant age-related co-morbidities appear as much as 10 years earlier compared with HIV-negative persons.[*5, 15] Earlier appearance of comorbidities in HIV infected individuals supports an earlier "older" age designation (i.e. 50 versus 65 years). The most common co-morbidities include hypertension, diabetes, cardiovascular disease, cancer, osteoporosis, frailty, cognitive decline, and hepatic and renal dysfunction.[*1, 16] The reasons for the earlier onset of these conditions are likely multifactorial, related in part to chronic immune activation from HIV and other chronic viral infections, life-style habits (smoking, alcohol, recreational drugs), and adverse effects from antiretroviral drugs.[2, 17] Chronic immune activation is also associated with frailty, which is a condition of vulnerability in older persons, often associated with a decline in muscle strength and depletion of end organ functional reserve.[18] This translates into heightened sensitivity to physiological stressors, which could include drug therapy, drug-drug interactions, or pharmacogenetic sensitivity to medications. Studies using a frailty-related phenotype have reported early occurrence and increased incidence of frailty in HIV infected individuals.[*6, 15] Frailty has been associated with pharmacokinetic changes and higher intra- and inter-patient pharmacokinetic variability.[14]

2.2 General pharmacology considerations for antiretroviral drugs

Twenty-five antiretroviral drugs from classes with six different mechanisms of action are currently available for clinical use.[*19] The classes and individual drugs exhibit wide variation in disposition and routes of elimination. Nucleoside analog reverse transcriptase inhibitors (NRTIs) are generally eliminated unchanged in urine, and require phosphorylation in cells, by cellular kinases and phosphotransferases, to elicit pharmacologic effect. Other drug classes undergo gut and hepatic metabolism. Cytochrome P450 3A plays the largest part in protease inhibitor metabolism, whereas 3A, 2B6, 2C9 and 2C19 are involved in the metabolism of non-nucleoside reverse transcriptase inhibitors (NNRTIs).[*19] The integrase inhibitors raltegravir and dolutegravir, which was recently submitted for regulatory approval, are predominantly metabolized by uridine 5′-diphospho-glucuronosyltransferase (UGT)-1A1. Antiretroviral drugs metabolized enterically and hepatically typically exhibit high protein binding to albumin and/or alpha-1 acid glycoprotein. Some antiretroviral drugs require an acidic environment for optimal dissolution and absorption (e.g. rilpivirine, atazanavir), and several antiretroviral drugs require special instructions for dosing relative to meals to optimize absorption. Numerous transporters contribute to the disposition and handling of all antiretroviral drugs in all classes, but this knowledge-base is still evolving. The proteins, enzymes, and transporters impacting antiretroviral drug pharmacokinetics, as well as absorption issues and dose adjustment requirements for hepatic or renal dysfunction are listed in Table 1 [Data from product information and refs [*19–22]]. Physiologic changes associated with aging or concomitant medications that impact any of these systems could alter antiretroviral drug pharmacokinetics in older patients.

2.3 Unique pharmacological characteristics for antiretroviral drugs

Antiretroviral drugs are always used in combination for optimal effectiveness, and recommended regimens consist of three active agents from at least two drug classes.[*19] Combination antiretroviral therapy increases the risk of drug-drug interactions. The protease inhibitors and elvitegravir (the newest integrase inhibitor) exhibit poor bioavailability and/or rapid systemic clearance predominantly through CYP3A, necessitating pharmacokinetic enhancing with ritonavir or cobicistat, CYP3A inhibitors. This raises the potential for drug-drug interaction with other therapies used in older patients. In the Swiss cohort study, older HIV infected persons (50 years) had 1.45-fold more potential drug-drug interactions compared with younger HIV infected persons (< 50 years), most notably for CNS and

cardiovascular drugs.[23] Some of the most powerful CYP3A-mediated drug interactions are between antiretroviral drugs and non-antiretroviral drugs, such as a 30-fold elevation in the area under the concentration time curve (AUC) observed for simvastatin when combined with ritonavir-saquinavir and a 49-fold elevation in AUC observed for vardenafil when combined with ritonavir.[24, 25] The general consensus is that older age does not impact the magnitude of drug inhibition interactions, but this has not been rigorously examined for antiretroviral drug interactions.[*26] One study evaluated the effect of chronic viral hepatitis (reduced hepatic reserve) on the magnitude of ritonavir inhibition of midazolam clearance as a surrogate for CYP3A activity. The subjects with chronic viral hepatitis had no difference in CYP3A activity compared with normal volunteers, but when receiving ritonavir, those with chronic viral hepatitis had half the CYP3A activity versus normal volunteers.[27] Thus, the inhibition effect of ritonavir was exaggerated when hepatic reserve was compromised by presence of chronic viral hepatitis. An analogous effect is possible with reduced hepatic reserve in older persons such as those with frailty phenotype.

Additional drug interaction potential arises from metabolic induction through activation of nuclear receptors such as pregnane X receptor (PXR) and constitutive androstane receptor (CAR) by protease inhibitors including ritonavir (inducers of CYP3A, 2B6 and UGT) and NNRTIs including efavirenz, etravirine, and nevirapine (inducers of CYP3A and/or 2B6). [28, 29] Some studies suggest that metabolic induction is blunted in older adults, although this finding is inconsistent.[*26, 30] One analysis of efavirenz autoinduction in 129 HIV infected persons from Tanzania, aged 39.6 ± 9.1 years, found no association between age and efavirenz autoinduction (efavirenz/M-8 metabolite ratio). [31] More information is needed for the effect of aging on antiretroviral drug induction.

Antiretroviral drugs also exhibit well-established pharmacokinetic-pharmacogenomic relationships that could manifest differently in older adults. For instance, in younger adults, CYP3A5 expressor-status (defined as those with at least one *1 allele versus only *3, *6, or *7 alleles) increases protease inhibitor oral clearance by approximately 30% in the absence of ritonavir boosting.[32–34] This CYP3A5 effect on atazanavir was retained in one study with ritonavir-boosting, but not in another study.[32, 35] CYP2B6 polymorphisms (e.g. 516 G>T and 983T>C) are associated with a significant loss of function and 3-fold elevations in efavirenz AUC.[36, 37] The bilirubin conjugating enzyme UGT1A1 metabolizes raltegravir and is inhibited by atazanavir.[38, 39] Homozygous UGT1A1*28 was associated with 40% higher raltegravir AUC, and several-fold greater bilirubin increases during atazanavir therapy.[38, 39] An evolving area in pharmacogenomics is the effect of polymorphisms in certain transport proteins in the gut, liver, and kidneys, such as ABCB1, ABCC2, ABCC4, SLCO1B1, etc, which may also impact clearance and distribution of antiretroviral drugs. [*40] Most studies of non-antiretroviral drugs suggest that pharmacogenetic changes are preserved in the elderly.[14, *26] This suggests that aging decrements in hepatic or renal function may add to decrements from pharmacogenetics, resulting in additive effects on clearance for antiretroviral drugs. However, this has not been adequately studied.

3. Pharmacokinetic-relevant physiological changes with age

Physiological declines associated with older age impact pharmacokinetics in multiple ways. A number of excellent reviews are available that summarize these aging-pharmacokinetic relationships.[*9, 14, *26, *41–43] Table 2 presents the general findings from these reviews in terms of aging effects on absorption, distribution, metabolism, and excretion. The potential influence on antiretroviral drugs, based on the pharmacology described in Table 1, is also provided.

Aging is associated with gastric changes such as increased pH, delayed gastric emptying time, decreased splanchnic blood flow, decreased gastrointestinal motility, and decreased

absorption surface. Additionally, potential reduced intestinal enzymes and transport proteins, such as CYP3A4 and ABCB1 (P-gp) would be important for antiretroviral drugs. [*9, 44] Such changes could result in slowed absorption rate and either reduced or enhanced bioavailability for antiretroviral drugs. Increased gastric pH may decrease absorption of antiretroviral drugs requiring acid for dissolution such as atazanavir and rilpivirine.[45] Conversely, lower CYP3A and Pgp content or function would theoretically increase bioavailability for substrates such as protease inhibitors, maraviroc, and some NNRTIs. Finally, as food intake changes in older persons (usually declining), dosing recommendations relative to meals could be affected.[46]

Aging is also associated with increased adiposity, lower lean body mass and total body water, decreased albumin, increased alpha-1-acid-glycoprotein, and potentially reduced drug transporter function, all of which can impact volume of distribution. [42, 44] Volume of distribution (Vd) determines loading doses (not relevant for antiretroviral drugs), half-life, and the shape of the concentration-time profile (peak and trough). The shape of the concentration time curve is important for antiretroviral drugs because target concentrations are typically troughs.[*19] Antiretroviral drugs, except NRTIs, have lipophilic characteristics, suggesting an increase in adipose tissue may increase Vd. In general, drugs with protein binding greater than 70% are considered sensitive to changes in protein binding (see Table 1). As albumin levels typically decline with age, whereas $alpha_1$-acid glycoprotein levels are unchanged or increased, it would be expected that drugs bound to albumin could exhibit an increased Vd in the elderly, while drugs bound to $alpha_1$-acid glycoprotein may show a decrease or no change in Vd. Little is known about the effects of age on drug transporter proteins. Small studies have found higher brain penetration of P-gp (ABCB1) substrate drugs in older persons, suggesting reduced P-gp activity at the level of the blood brain barrier.[47, 48] Increased antiretroviral drug penetration into the brain could be beneficial for patients suffering from HIV-associated neurocognitive disorders, which is an important co-morbidity in older persons.[49] Conversely, higher brain penetration could also be detrimental if associated with higher CNS toxicities, which are potential concerns for efavirenz and rilpivirine.[*19] Additional studies are needed to understand the influence of age on transporters and antiretroviral drug distribution into the brain and other important tissues such as the gut, kidney, and liver.

Aging is associated with reduced hepatic function, and potentially impaired drug clearance, which is the most important pharmacokinetic parameter because it determines average steady-state concentrations. The liver is the chief drug metabolizing organ, although the intestines, kidneys, and other tissues contribute as well. Reduced liver mass, decreased hepatic blood flow, and changes in plasma protein binding impact hepatic clearance in the elderly.[*9, *26] Protein binding changes impact the availability of drug for metabolism, depending on the rate limiting process for clearance (i.e. blood flow or metabolic activity). Oral plasma clearance (CL/F) for both flow and metabolism limited drugs is rate-limited by intrinsic clearance (CLint) and the fraction unbound in plasma (Fu), that is CL/F~CLint*Fu. [*41, 50] Both CLint and Fu can change in older people, sometimes in opposite, offsetting directions (↓CLint and ↑Fu), especially for drugs bound to albumin.[*41] This could result in relatively unchanged oral clearance (CL/F ~ ↓CLint * ↑Fu) based on total drug concentrations, but slower CLint and significantly higher unbound, pharmacologically-active concentrations.[*41] Put another way, changes in protein binding in older people may mask slower CLint. This has been proposed to explain why some studies do not find age associated changes in CL/F.[*41] When studies have accounted for protein binding changes in older people, the unbound clearance (CLint) for both phase I and phase II metabolized drugs were consistently diminished in older people by 30%-50%.[*41]

Intrinsic clearance (CLint) depends upon maximal metabolic enzymatic capacity (Vmax) and drug affinity for the metabolizing enzyme (Km). CLint for first order metabolism is approximately, Vmax/Km. Vmax is proportional to liver size, which is decreased up to ~30% with older age.[*9, 51, 52] A smaller liver and reduced Vmax would decrease intrinsic clearance for oral hepatically metabolized drugs in older persons. General CYP450 clearance has been shown to diminish by up to 30% after age 65 as measured by antipyrine clearance, a broad spectrum CYP450 probe. [53] Most evidence supports similar reductions in CL/F in the older adults for CYP3A substrates, and 20% lower clearance has also been reported for buproprion, a 2B6 substrate, in older adults.[54, 55] These findings suggest that antitretroviral drugs will be similarly affected by older age given the importance of CYP3A and 2B6 on their clearance (Table 2).

Uncertainty surrounds the impact of age on phase II metabolized drugs. Multiple review papers conclude that phase II metabolism is preserved in older persons, but other studies suggest declines in metabolism. In one comprehensive review, the AUCs for drugs that undergo glucuronidation were approximately 1.4 fold higher in older versus younger persons.[56] Further, the review of protein binding effects described above showed diminished phase II clearance in older people after accounting in changes in protein binding. [*41] This suggests that age could influence the clearance of several antiretroviral drugs that undergo substantial glucuronidation (Table 2).[57]

Perhaps the most important age-related change that impacts pharmacokinetics is reduced renal function. Physiological changes include decreased glomerular filtration rate (GFR), decreased kidney mass, decreased nephron size and number, decreased glomerular surface area, decreased tubular function, and decreased renal blood flow.[42] As a consequence, both renal secretion and GFR decline with age. Age is a critical variable in the Cockroft-Gault and Modified Diet in Renal Disease (MDRD) equations used to estimate GFR for drug dosing.[58] Renal function is particularly relevant for NRTIs, such as tenofovir and emtricitabine, which undergo substantial renal elimination, requiring dose adjustments with renal dysfunction.[59, 60]

4. Data specific to PK and ARV drugs in elderly

The most important consideration for drug dosing in the elderly is to assess potential drug-drug interactions, and hepatic and renal function, and to follow dosing recommendations based on these parameters (Table 1).[*19] In the absence of dosing guidance, clinicians should refer to pharmacokinetic data to guide therapy in the elderly. To date, few well-controlled prospective studies have assessed antiretroviral pharmacokinetics in the elderly. One prospective pharmacokinetic study in older adults evaluated a single dose of atazanavir in 60 HIV-negative adults stratified by gender and age. The mean (range) ages were approximately 70 years (65 to 81) versus 27 (19 to 39), balanced by gender. The maximum concentration (Cmax) and AUC were ~17% higher in older adults (90% CI −5% to 45%), which was partially contained in the 90% CI, but statistically inconclusive.[61] The study did not quantify the effect of ritonavir-boosting on atazanavir concentrations, protein binding, or steady-state conditions, which are all important considerations. Another prospective study measured lopinavir trough concentrations in antiretroviral naïve HIV infected adults aged 18 to 30 (n=37) versus aged 45 to 79 (n=40).[62] A population pharmacokinetic model predicted that lopinavir clearance would decrease 38% from 20 years to 80 years (P=0.025), after adjusting for adherence, which was higher in older versus younger participants. Again, protein binding was not evaluated in this study. A third prospective study compared lamivudine pharmacokinetics in 6 elderly males > 65 years versus 6 younger males (note, the original manuscript was not available to the authors).[63]

The AUC was 1.4-fold higher in those > 65 years, which was attributed to reduced renal clearance.

In addition to these limited prospective studies, we evaluated 73 retrospective pharmacokinetic studies in adults that evaluated age as a covariate. These studies were population pharmacokinetic analyses or observational studies including either intensive sampling for AUC measurements, or single time points (e.g. peaks, midpoint concentrations, and/or troughs). Statistical analyses typically used standard regression approaches. Population pharmacokinetic studies typically compared objective functions from nested models with age as a covariate versus a base model with no covariates. Most studies used multivariate analyses. The studies reported various age distributions; most reported median (range). For those that reported mean (standard deviation) or median (interquartile range), we converted these to mean or median (± 2 standard deviations), assuming a normal distribution. In combination, these studies evaluated over 13,000 adult patients with a median (range) age of approximately 40 (22 to 62) years. Table S1 provides a summary of findings.[20, 64–136]

4.1 Cell entry and integrase inhibitors

No associations were observed between age and plasma maraviroc (n=538) or enfuvirtide (n=534).[65, 101, 108, 128] One study found a faster distribution rate for maraviroc in older persons, but this did not impact AUC.[65] Similarly, no associations were observed for age and integrase inhibitor pharmacokinetics including raltegravir (n=250) and elvitegravir (n=534).[73, 120, 129]

4.2 NNRTI

One population pharmacokinetic study of delavirdine (n=234) showed a correlation between age and intrinsic clearance, but the magnitude was not reported and the correlation did not explain a large portion of pharmacokinetic variability.[74] Twelve studies evaluated the association between age and efavirenz pharmacokinetics and no significant age effects were observed (n=1755). Two reported an age effect in the uni-variate analysis, but age was not retained in multi-variate models.[66, 75] One large population pharmacokinetic study of etravirine (n=577) found no influence of age on etravirine pharmacokinetics, whereas another (n=190) showed 5% higher AUC per decade of age.[70, 130] Twelve studies evaluated age as a covariate with nevirapine pharmacokinetics (n=1461). Four identified a relationship between age and clearance. One found an increase in clearance of 1.56% per year after 35 years of age (35 being the median age in the study).[97] Two studies found declines in clearance with age and one reported a correlation between age with nevirapine concentrations, without reporting the magnitude or direction.[20, 103, 124] One large population pharmacokinetic study of rilpivirine (n=679) did not find an association between age and rilpivirine pharmacokinetics.[131]

4.3 PIs

Nine studies evaluated the association of lopinavir pharmacokinetics with age (n=3065), eight studies found no associations in the final models. One study (n=30) found a predicted 100% increase in lopinavir AUC from 25 to 60 years.[85] Similarly, nine studies evaluated atazanavir pharmacokinetics (both with and without ritonavir) for associations with age, and eight found no assoiactions (n=1138). One small study of only unboosted atazanavir (n=31) found a slower atazanavir clearance with age over 30.[132]

Twenty-three studies evaluated the association between age with pharmacokinetics for amprenavir (2), darunavir (3), indinavir (6), nelfinavir (3), ritonavir (7), and saquinavir (2). Of these, one study with saquinavir showed slower clearance with age, but the magnitude

was not reported.[94] One observational pharmacokinetic study with indinavir (n=46) showed a parabolic relationship between concentrations and age (concentrations increased from 40 to 50 years, then decreased from 50 to 60 years).[92] However, a population pharmacokinetic study with the same patient cohort found no age effect.[137] Another population pharmacokinetic study of indinavir (n=171) found increased volume in older persons, with no effect on clearance.[104] All the ritonavir studies were negative for age effects except one that showed a faster elimination rate in middle aged (40 years) versus younger adults (20 years).[109] Two of three darunavir population PK studies reported slightly higher AUC with age.[130, 134] Two of three nelfinavir studies showed reduced M8 metabolite concentrations in older adults. M8 is generated by CYP2C19 and cleared by CYP3A. Finally, two studies were not included in the table because age ranges were not reported: one showed no association between age and ritonavir-boosted fosamprenavir (n=61), and the other showed stable tipranavir troughs in older adults. [138, 139]

4.4 NRTI

Of the NRTIs, abacavir is predominantly metabolized in the liver. Two population pharmacokinetic studies found no age association with abacavir pharmacokinetics (n=229). [135, 136] All other NRTIs undergo renal excretion and require dose adjustments for reduced renal function (Table 1). Age, creatinine clearance, and/or serum creatinine correlated with tenofovir or lamivudine clearance in 6 of 7 studies.[68, 79, 80, 107, 117, 126] No studies with emtricitabine were identified, but its renal elimination is similar to lamivudine and tenofovir (~70% unchanged drug in urine). No relationships were identified between age and didanosine pharmacokinetics (2 studies, n=254) or stavudine pharmacokinetics (2 studies, n=120).[81, 87, 110, 111] Four studies evaluated zidovudine (n=348), and two identified relationships with age: one reported slower clearance in younger adults less than 30 years, the other reported decreased clearance in those over 50 years.[94, 111] No relationships were reported between active NRTI-triphosphate concentrations in peripheral blood mononuclear cells with age.[68, 79]

5. Other considerations for older HIV infected individuals

In general, older HIV infected individuals have better adherence to antiretroviral drugs, however an increase in cognitive impairment with aging could present problems with adherence.[*140, 141] Virologic responses are often better in older HIV infected persons even after controlling for adherence, suggesting that different pharmacokinetics may drive better antiviral responses.[*9, 44] Despite this better virologic response, older patients tend to have blunted CD4 responses, indicating impaired immunologic reserve.[*9] For this reason, guidelines recommend that older patients over 50 years of age should begin antiretroviral therapy as soon as possible regardless of CD4 count.[*19]

Older HIV-infected patients appear to experience more toxicities with antiretroviral drugs, including hematologic, lipid, and central nervous system, which might suggest higher drug concentrations, or a lower physiological reserve.[*1, *140, 142, 143] An increased risk of drug toxicities in older persons in the general population provides the impetus for the Beers criteria for "potentially improper medications" in the elderly.[*144] These criteria provide a list of medications to avoid in older adults, including those increasing the risk of orthostatic hypotension, QT-interval prolongation, and central nervous system side effects. Among antiretroviral therapies, these same side effects are important concerns for efavirenz (CNS side effects), saquinavir (QT-interval prolongation), and maraviroc (postural hypotension with renal dysfunction). These antiretroviral medications should be used cautiously in the elderly.

The future study of antiretroviral drugs in older persons must include more controlled prospective pharmacokinetic studies with attention to plasma protein-binding.[*41] This is particularly important for antiretroviral drugs with high binding to albumin, such as efavirenz. Although none of 12 studies reported in Table S1 identified an association between age and efavirenz concentrations, only total efavirenz concentrations were measured. To illustrate how protein binding can mask intrinsic clearance changes, we simulated concentration-time profiles for two theoretical populations, young versus older patients where intrinsic clearance was assumed to be ~50% in the older group, but binding to albumin was also decreased (fu increased by ~50%). These effects would offset the total CL/F (CL/F~↓CLint*↑fu) and result in similar total drug concentrations, but increased unbound drug concentrations, potentially leading to toxicity (Figure 1).

Other antiretroviral drugs bind more avidly to alpha-1-acid-glycoprotein (Table 2), which may increase in older adults, especially in those with inflammatory conditions.[42,44] In the setting of increased binding, total clearance would decrease and total drug concentrations would increase (↓CL/F~CLint*↓fu). If CLint were decreased as well, total clearance would be reduced further, and total drug concentrations would be increased further (↓↓CL/F~↓CLint*↓fu). However, changes in total drug concentrations were not frequently observed among older adults in the studies described in Table S1, suggesting that this scenario was not playing out in the age ranges of these studies (~20 to 60 years).

6. Conclusion

Over the coming years, increasing numbers of older HIV infected people will be treated with antiretroviral medications, but there is little guidance on how to use antiretroviral therapy safely and effectively in this population. Aging is associated with numerous physiological changes that could impact antiretroviral drug pharmacokinetics. However, there is little evidence to date of clinically relevant changes in antiretroviral drug pharmacokinetics in HIV infected patients between ~ 20 and 60 years. Until more information is available in those > 60 years of age, the best course of action is to follow dosing guidelines based upon drug-drug interactions, and renal and hepatic function.

7. Expert opinion

Most pharmacokinetic data in older persons arise from retrospective observational analyses and population pharmacokinetic studies where patient ages ranged from ~20 to 60 years. These studies show that NRTIs, like other renally eliminated drugs, undergo pharmacokinetic changes as renal function declines. This is relevant for older adults, as approximately half of elderly adults have GFR < 60 mL/min per 1.73 m^2.[145] The studies of hepatically cleared drugs do not support consistent, reproducible, substantial changes in pharmacokinetics in the participant age ranges of the studies (~20 to 60 years). Of note, these age ranges encompass the "older" age definition of 50 years for HIV infected individuals, suggesting that pharmacokinetics of liver metabolized antiretroviral drugs are minimally changed in HIV infected individuals at this "older" age definition. This includes drugs metabolized by CYP3A (protease inhibitors, rilpivirine), CYP2B6 (efavirenz, nevirapine), CYP2C9/2C19 (etravirine) UGT1A1 (raltegravir), and UGT2B7 (zidovudine). The most important limitations of these studies are the retrospective design, the limited number of subjects at the extremes of older age, probable exclusion of those with frailty or significant comorbidities, and the absence of protein binding measurements. Because of these limitations, these studies should not be the sole basis for decision-making when treating older HIV infected patients > 60 years of age. Additional studies are needed in more people > 60 years old, and in those with frailty and/or significant comorbidities. Future

studies should also include an assessment of protein-binding, drug-drug interactions, and pharmacogenetics in older persons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- HIV infected individuals are reaching older ages in high numbers

- Older HIV infected individuals experience frailty and co-morbidities at earlier ages and with higher incidences compared with non-HIV infected individuals.

- Older age is associated with reduced renal and hepatic function, and polypharmacy, but few prospective pharmacokinetic studies have been conducted in older HIV infected individuals.

- Retrospective studies do not support consistent, reproducible, substantial changes in pharmacokinetics of hepatically eliminated drugs in the age ranges of ~20 to 60 years.

- Renal function should be assessed in older HIV infected individuals and dose adjustments made based upon renal function.

- Additional studies are needed in more HIV infected individuals > 60 years old, and in those with frailty and/or significant comorbidities
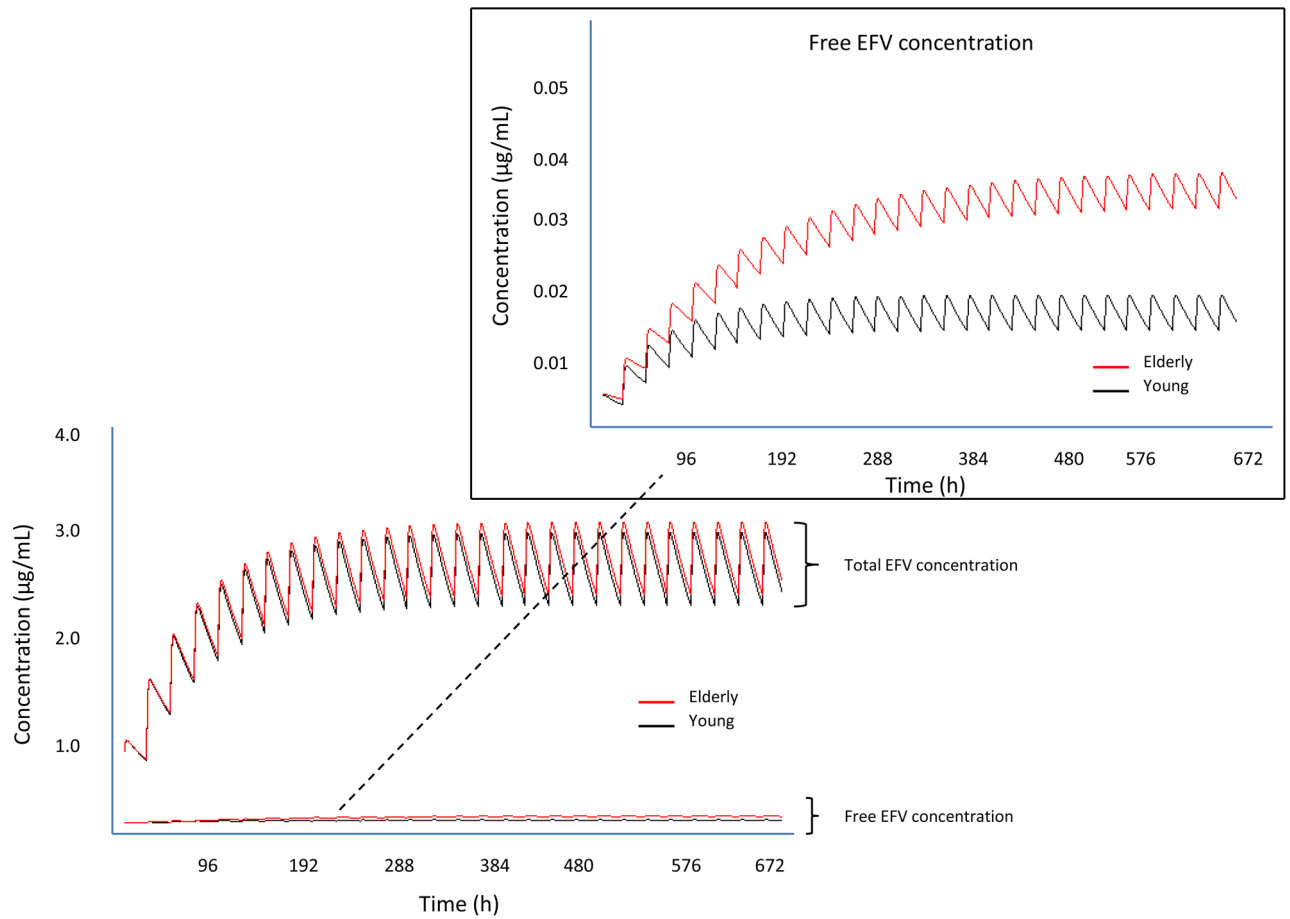
Figure 1.
Simulation of total and unbound (inset) efavirenz concentrations in young (light color) versus older adults (dark color) where intrinsic clearance in older individuals was assumed to be half that in younger adults, but unbound fraction was also assumed to be higher in older adults. Data for simulations were obtained from the product information.

Table 1

General pharmacologic considerations for antiretroviral drugs [Data from product information and [19–22]]

Antiretroviral drug class (agents)	Absorption considerations[a]	% unchanged in urine	Metabolism Routes (as a class)	Renal/hepatic dose adjustments?[b]	Transporter proteins substrates (as a class)	Plasma protein binding[c]
Pharmacokinetic enhancer (cobicistat)	None[d]	8.2%	CYP3A, CYP2D6	Renal: Yes[d] / Hepatic: No	pending	97.5%
CCR5 inhibitor (maraviroc)	None	8%	CYP3A4	Renal: Yes / Hepatic: No	ABCB1, OATP1B1	76%
Fusion inhibitor[e] (enfuvirtide)	N/A	N/A	N/A	Renal: No / Hepatic: No	N/A	92% (predominantly albumin)
Integrase inhibitors (raltegravir) (elvitegravir)	**Raltegravir:** None **Elvitegravir:** ↑ with food	6.7 to 9%	UGT1A1, CYP3A4	Renal: Yes[d] / Hepatic: No	ABCB1, OAT1	83% to >98%
NNRTI (efavirenz) (delavirdine) (etravirine) (nevirapine) (rilpivirine)	**Efavirenz:** ↑ with food[f] **Delavirdine:** None **Etravirine:** ↑ with food **Nevirapine:** None **Rilpivirine:** ↑ with food, ↓ with antacid	< 5%	CYP2B6, CYP3A, CYP2C9, CYP2C19, UGT2B7	**Efavirenz:** Renal: No / Hepatic: Yes **Delavirdine:** Renal: N/E / Hepatic: N/E **Etravirine:** Renal: No / Hepatic: No **Nevirapine:** Renal: No (if CrCL >20 mL/min) / Hepatic: Yes **Rilpivirine:** Renal: No / Hepatic: No	ABCB1, ABCG2, ABCC1, ABCC2, ABCC10	**Efavirenz:** 99.5–99.75% (mostly albumin) **Delavirdine:** 98% (mostly albumin) **Etravirine:** 99.6% albumin 97.66–99.02% AAG **Nevirapine:** 60% **Rilpivirine:** 99.7%
NRTI (abacavir) (zidovudine) (tenofovir) (emtricitabine) (lamivudine) (didanosine) (stavudine)	**Abacavir:** None **Zidovudine:** None **Tenofovir:** None **Emtricitabine:** None **Lamivudine:** None **Didanosine:** ↓ with food **Stavudine:** None	**Abacavir:** 1.2% **Zidovudine:** 29% **Tenofovir:** 75% **Emtricitabine:** 86% **Lamivudine:** 71% **Didanosine:** 42% **Stavudine:** 74%	UGT2B7 ADH	**Abacavir:** Renal: No / Hepatic: Yes **Zidovudine:** Renal: Yes / Hepatic: Insufficient data **Tenofovir:** Renal: Yes / Hepatic: No **Emtricitabine:** Renal: Yes / Hepatic: No **Lamivudine:** Renal: Yes / Hepatic: No **Didanosine:** Renal: Yes / Hepatic: No **Stavudine:** Renal: Yes / Hepatic: No	ABCB1, ABCC1, ABCC2, ABCC4, ABCC10, ABCG2, OCT1-3, OAT1-3	**Abacavir:** 50% **Zidovudine:** <38% **Tenofovir:** <0.7% **Emtricitabine:** <4% **Lamivudine:** <36% **Didanosine:** <5% **Stavudine:** Negligible

Antiretroviral drug class (agents)	Absorption considerations[a]	% unchanged in urine	Metabolism Routes (as a class)	Renal/hepatic dose adjustments?[b]	Transporter proteins substrates (as a class)	Plasma protein binding[c]
Protease inhibitors (atazanavir) (indinavir) (darunavir) (tipranavir) (lopinavir) (saquinavir) (fosamprenavir) (ritonavir) (nelfinavir)	**Atazanavir:** ↑ with food, ↓ with antacid **Indinavir:** ↓ with food **Darunavir:** ↑ with food **Tipranavir:** None **Lopinavir:** Formulation dependent[g] **Saquinavir:** ↑ with food **Fosamprenavir:** None **Ritonavir:** ↓ with food[f] **Nelfinavir:** ↑ with food	**Atazanavir:** 7% **Indinavir:** 19% **Darunavir:** 8% **Tipranavir:** 0.5% **Lopinavir:** 2% **Saquinavir:** 1% **Fosamprena vir:** 1% **Ritonavir:** 3.5% **Nelfinavir:** 1.5%	CYP3A, CYP2C19	**Atazanavir:** Renal: No Hepatic: Yes **Indinavir:** Renal: No Hepatic: Yes **Darunavir:** Renal: No Hepatic: No **Tipranavir:** Renal: No Hepatic: Yes **Lopinavir:** Renal: No Hepatic: No **Saquinavir:** Renal: No Hepatic: No **Fosamprenavir:** Renal: No Hepatic: Yes **Ritonavir:** Renal: No Hepatic: No **Nelfinavir:** Renal: No Hepatic: Yes	ABCB1, ABCC1, ABCC2, OATP1A2, OATP1A3, OATP1B1	**Atazanavir:** 86% albumin 89% AAG **Indinavir:** 60% **Darunavir:** 95% (predominantly AAG) **Tipranavir:** >99.9% **Lopinavir:** 98.5% (predominantly AAG) **Saquinavir:** 98% **Fos(amprena vir):** 90% **Ritonavir:** 98.5% **Nelfinavir:** >98%

N/A=not applicable; N/E=not evaluated; AAG=alpha-1-acid glycoprotein; ADH=alcohol dehydrogenase; CYP=cytochrome P450; ABC=ATP binding cassette transporter; OATP=organic anion-transporting polypeptide; OAT= organic anion-transporter; OCT=organic cation-transporter; other letters/numbers refer to specific isozymes.

[a] The effect of food on absorption was not indicated unless the impact was significant enough to require specific administration recommendations with respect to food. This same approach was applied to concomitant antacid use.

[b] Most ARV drugs have not been evaluated in patients with severe hepatic impairment. "No" refers to patients with mild to moderate (Child Pugh A or B) hepatic impairment. "Yes" indicates that there may be dosing adjustments or that use in moderate to severe (Child Pugh B or C) is not recommended

[c] Where specific distributions in protein binding for albumin and AAG were available, these were indicated. Where not available, the % shown indicates the overall plasma protein binding.

[d] Cobicistat and elvitegravir are co-formulated with tenofovir and emtricitabine, which require dose adjustments with renal dysfunction. Due to increased absorption of elvitegravir with food, Stribild® should be taken with food

[e] Enfuvirtide is cleared via protein catabolism

[f] Efavirenz is recommended on an empty stomach and ritonavir with a meal to reduce adverse effects.

[g] The absorption of the tablet formulation is not significantly altered by food, whereas absorption of the solution formulation is increased in the presence of food

Table 2

Potential Impact of Age Related Changes on Pharmacokinetics

PK Parameter	Age Related Change affected PK parameter	PK Impact	Predicted overall PK effect	Examples of potential HIV drugs affected
Absorption (ka, F)	↑ gastric pH ↓ gastric emptying ↓ splanchnic blood flow ↓ intestinal CYP3A4 ↓ intestinal P-gp	↓ F ↔ F, ↓ Ka ↔ F, ↓ Ka ↑ F ↑ F	↓ F or ↑ F ↓ Ka	Atazanavir Rilpivirine Other PIs Maraviroc
Distribution (Vd)	↓ albumin ↑ α-1-acid-glycoprotein ↑ body fat composition ↓ lean muscle and total body water ↓ transport protein activity	↑ Vd ↓ Vd ↑ Vd[a] ↑ Vd	↑ Vd	NNRTI PIs Maraviroc
Metabolism (CL)	↓ albumin ↑ α-1-acid-glycoprotein ↓ liver mass (↓ Vmax) ↓ hepatic blood flow	↑ CL/F ↓ CL/F ↓ CL/F ↔ CL/F	↓ CL/F	PIs NNRTIs Maraviroc InSTI
Excretion (CL)	↓ renal function ↓ transport processes	↓ CL/F ↓ CL/F	↓ CL/F	NRTI

Ka = absorption rate constant, F = bioavailability, Vd = volume of distribution, CL/F = apparent oral clearance, PI = protease inhibitors, InSTI = integrase strand transfer inhibitor

[a]An increase in Vd would be expected for lipophilic drugs; lipophilicity is assumed for hepatically metabolized medications.