Antiretroviral therapy in older people with HIV

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Purpose of review
The age of people with HIV continues to rise, and yet older people have tended to be under-represented or excluded from premarketing studies of antiretroviral therapy (ART). In this review, we highlight special considerations for the use of ART in older people with HIV, with a focus on toxicities associated with specific antiretroviral agents or drug classes as well as key research questions moving forward.

Recent findings
Like all people with HIV, older people with HIV should be started on ART as soon as possible, regardless of CD4 count, and with a regimen that includes an integrase strand transfer inhibitor (INSTI) and two nucleoside reverse transcriptase inhibitors. Important toxicities to consider when choosing an ART regimen include bone and renal effects related to tenofovir, weight gain related to INSTIs and tenofovir alafenamide, neurocognitive and neuropsychiatric toxicities related to efavirenz, and increased cardiovascular risk associated with abacavir and boosted protease inhibitors. With the ongoing importance of INSTIs as a component of preferred ART regimens, further characterization of INSTI-related weight gain is a critical current research priority in understanding ART toxicity.

Summary
There are multiple potential toxicities of ART to consider when selecting a regimen for older people. Specific agents or drug classes have been implicated in adverse bone or renal effects, weight gain, neuropsychiatric and neurocognitive effects, and cardiovascular risk.

Keywords
aging, antiretroviral therapy, drug toxicities, HIV, older adults

INTRODUCTION
Over the two-plus decades since combination antiretroviral therapy (ART) first proved effective at durably suppressing replication of HIV and improving survival, the age of people with HIV has risen substantially. In the United States in 2016, 48% of people with HIV, and 17% of those newly diagnosed with HIV, were over the age of 50 years \cite{1}. Globally, 7.5 million people with HIV are over the age of 50 years, representing about 20% of all people with HIV \cite{2}. With the HIV population growing older over time, there has been increased attention paid in recent years to aspects of clinical care that are unique or particularly important in the management of older people with HIV \cite{3}. In this review, we highlight special considerations for the use of ART in older people with HIV, with a focus on toxicities associated with specific antiretroviral agents. Polypharmacy and the potential for drug–drug interactions are also important factors when selecting ART for older people with HIV; these topics are discussed elsewhere \cite{4}.

WHEN TO INITIATE ANTIRETROVIRAL THERAPY
All major treatment guidelines recommend ART for all people with HIV, regardless of CD4 T-cell count \cite{5–7}. Early and expeditious initiation of ART is especially important in older people. Older people with HIV are more likely to have non-HIV comorbidities and multimorbidity \cite{8,9}, putting them at greater risk of the serious non-AIDS diseases and complications that are major drivers of mortality in the setting of HIV treatment delay or interruption \cite{10}. In addition, although older people with HIV have higher rates of viral suppression (probably mediated by increased overall adherence), they tend...
to have lower CD4 T-cell counts at diagnosis [11], and the immunologic response to ART decreases with age, manifesting in poorer CD4 T-cell count recovery [12–15].

SELECTING AN ANTIRETROVIRAL THERAPY REGIMEN

Treatment guidelines in the United States, Europe, and globally, recommend an initial ART regimen that in most cases includes an integrase strand transfer inhibitor (INSTI) and two nucleoside reverse transcriptase inhibitors (Table 1) [5–7].

INSTIs are generally preferred over nonnucleoside reverse transcriptase inhibitors (NNRTIs) and boosted protease inhibitors because they have been found in randomized controlled studies (RCTs) to be equivalent or superior in terms of viral efficacy and tolerability to the NNRTI efavirenz (EFV) and the boosted protease inhibitors ritonavir-boosted atazanavir (ATV/r) and ritonavir-boosted darunavir (DRV/r) [16–20]. Dolutegravir (DTG) and bictegravir (BIC) are the preferred INSTIs because they have a higher barrier to resistance compared with elvitegravir (EVG) and raltegravir (RAL), and furthermore do not require a boosting agent.

Options for NRTI combinations include tenofovir alafenamide-emtricitabine (TAF/FTC), tenofovir disoproxil fumarate-emtricitabine (TDF/FTC), and abacavir-lamivudine (ABC/3TC). Of these, tenofovir-containing combinations are preferred over ABC/3TC because of superior safety and tolerability, and because they can be given regardless of HLA-B*5701 or hepatitis B status [21–24]. TAF/FTC is generally preferred over TDF/FTC because of a more favorable renal and bone toxicity profile (detailed below) with comparable virologic efficacy. With the growing data on the use of DTG/3TC as an effective treatment option, the utility of abacavir in an older patient population is unclear, as previously it might have been used for patients with renal or bone disease.

Table 1. Preferred initial antiretroviral therapy for most adults with HIV include an integrase strand transfer inhibitor and two nucleoside reverse transcriptase inhibitors

<table>
<thead>
<tr>
<th>United States Department of Health and Human Services (DHHS) and European AIDS Clinical Society (EACS) guidelines [5,6]</th>
<th>WHO guidelines [7]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir with tenofovir/emtricitabine (DTG + TAF/FTC or TDF/FTC)</td>
<td>Dolutegravir with lamivudine (or emtricitabine) with tenofovir disoproxil fumarate (DTG + 3TC or TDF + TDF)</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) – If HLA-B*5701 negative</td>
<td>Bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC)</td>
</tr>
<tr>
<td>Bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC)</td>
<td>Raltegravir with tenofovir/emtricitabine (RAL + TAF/FTC or TDF/TFC)</td>
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TOXICITIES OF ANTIRETROVIRAL THERAPY

As people age, they are more likely to experience adverse effects of treatments and may not live long enough to accrue the full benefits, particularly for medications serving a primary or secondary prevention purpose [25]. In HIV, the benefits of viral suppression over both the short-term and long-term outweigh the risks of ART in virtually all circumstances. With the current availability of many ART combinations that can effectively treat HIV, clinicians must consider the relative toxicities of the various ART components when selecting an optimal regimen. This is especially important for older people with HIV, who tend to have more comorbidities and organ dysfunction, and thus are more vulnerable to clinically meaningful toxicities related to ART. Furthermore, premarketing studies of ART have tended to under-represent older people. As a result, the pharmacokinetics and pharmacodynamics of ART in older people (who often have alterations in drug absorption, metabolism, and excretion), as well as the potential for adverse effects, are less...
BONE TOXICITIES

People with HIV have a substantially higher risk of osteoporosis and bone fracture compared with those without HIV, and this risk increases considerably with older age [26]. TDF, a pro-drug of the nucleotide analogue tenofovir diphosphate, leads to greater decreases in bone mineral density relative to other NRTIs, and should be avoided if possible in older people and other patients at higher risk for fragility fracture [27]. In an RCT of ART-naive participants with HIV, regimens containing TDF/FTC had greater reductions in bone demineralization after 24 months compared with those containing ABC/3TC [28].

Tenofovir alafenamide (TAF) has higher intracellular penetration than TDF, thus requiring a lower dose with lower plasma levels. As a result, TAF has a more favorable bone toxicity profile. Two large RCTs of ART-naive participants with 24–36 months of follow-up found that participants receiving TAF-containing regimens had significantly less bone demineralization than those receiving TDF when used in combination with the INSTI DTG or cobicistat-booster elvitegravir (EVG/c), or the NNRTI EFV [29,30*]. In two ART switch studies, where participants with HIV on ART who had already achieved viral suppression were randomized to continue TDF or change to a TAF-containing regimen, participants receiving TAF had improvements in bone parameters relative to those receiving TDF [31,32*]. Older people are better represented in switch studies, which by definition include only treatment-experienced participants. Findings from a recent meta-analysis of 11 RCTs suggest that the difference in bone demineralization between TDF-containing and TAF-containing regimens may be partially explained by the simultaneous use of a pharmacokinetic booster (cobicistat or ritonavir) [33**].

Recent data suggest that dual therapy with DTG and 3TC is effective, potentially obviating the need for tenofovir (and subsequent bone toxicity) altogether, except for patients who have chronic hepatitis B or known or suspected resistance to 3TC. Two RCTs—one including ART-naive participants and one including participants on DTG and TAF/FTC without history of treatment failure or viral resistance—have shown that DTG and 3TC is noninferior to DTG and TAF/FTC [34*,35].

There is also evidence that boosted protease inhibitors are associated with greater reduction in bone mineral density. Some of this effect may be related to concomitant TDF use, as highlighted by one RCT, which included TDF/FTC for all participants and compared the INSTI raltegravir (RAL) to a boosted protease inhibitor—either ATV/r or DRV/r [36]. However, increased bone demineralization with boosted protease inhibitors has also been found in an RCT comparing boosted protease inhibitor-containing regimens with NNRTI-containing regimens [37], and in a large cohort study that controlled for TDF use [38]. For this reason, in addition to other toxicities and potential drug interactions, boosted protease inhibitors should be avoided if possible in older people and others either with or at high risk for low bone density [27].

RENA L TOXICITIES

Older age has consistently been shown to be an independent risk factor for development of kidney disease in people with HIV [39–41]. As with bone toxicity, TDF is the primary cause of renal toxicity among antiretrovirals. TDF use is associated with progression of chronic kidney disease (CKD), mediated by a proximal tubular nephropathy, which can rarely manifest as Fanconi syndrome [39,42–45]. Older age itself is an independent risk factor for TDF toxicity [46]. Randomized controlled trials of ART-naive participants have found worsened renal biomarkers and higher rates of renal adverse events or discontinuations over 12–24 months of follow-up for TDF/FTC-containing regimens compared with ABC/3TC (particularly when paired with ATV/r) or TAF/FTC [29,30**,47,48]. Switch trials from TDF-containing to TAF-containing regimens have similarly found improvements in renal markers and fewer renal adverse events in the TAF groups [31,32*]. As with bone effects, the renal adverse effects of TDF, including Fanconi syndrome, are less common when not co-administered with a pharmacokinetic booster [33**,49]. If possible, clinicians should avoid TDF use in older people and others at risk of CKD. In addition, as discussed above, dual therapy with DTG and 3TC is an attractive tenofovir-sparing option [34*,35].

Some protease inhibitors have also been associated with kidney disease. In one large cohort study, ATV and ritonavir-boosted lopinavir (LPV/r) were found to be associated with CKD, independent of TDF use [39]. In one study of patients on ATV/r or LPV/r, switching to DRV/r improved kidney function [50].

Several antiretroviral agents inhibit tubular creatinine secretion, thereby increasing measured serum creatinine; importantly, this does not indicate a reduction in glomerular function. This effect is most pronounced with dolutegravir and cobicistat, and occurs to a slightly lesser degree with
bicitravir, rilpivirine, and ritonavir [51]. Clinicians should expect a rise in creatinine in patients receiving these drugs, but understand that does not necessarily represent renal toxicity. In general, an increase of 0.4 mg/dl or less can be considered benign, especially if this is without abnormalities in urinary protein or glucose [52].

**NEUROCOGNITIVE AND NEUROPSYCHIATRIC TOXICITIES**

Some studies suggest HIV-associated neurocognitive disorder (HAND) is common and under-recognized [53], even with effective ART, and older age has consistently been associated with worse neurocognitive function in HIV [54–57]. Efavirenz, which until recently was a preferred agent for inclusion in combination ART, induces both neuropsychiatric and neurocognitive adverse effects. There is a dose-dependent relationship between EFV and acute psychosis, nightmares, irritability, and concentration defects [58]. The most pronounced symptoms typically resolve within weeks of initiating therapy [59,60] but many individuals continue to have some neuropsychiatric side effects even with long-term therapy. A pooled analysis of four randomized controlled studies (RCTs) found that EFV is independently associated with a long-term increase in risk of suicidality [61], an effect that was augmented in those who metabolize the drug more slowly [62]. Multiple studies have also found that EFV is associated with long-term neurocognitive deficits, particularly in older people [63,64]. Importantly, not all studies of EFV implicate the drug as causing adverse neurocognitive effects. A recent large cohort study with extensive longitudinal neuropsychological testing found no difference in neurocognitive functioning between patients receiving EFV and those who never received EFV [65**].

Several randomized studies have evaluated the differential effects of EFV versus other agents on neuropsychiatric side effects, both as initial therapy and as a switch strategy. In aggregate, initial therapy with non-EFV regimens leads to fewer neuropsychiatric side effects, both as initial therapy and as a switch strategy. In aggregate, initial therapy with non-EFV regimens leads to fewer neuropsychiatric side effects, both as initial therapy and as a switch strategy. In aggregate, initial therapy with non-EFV regimens leads to fewer neuropsychiatric side effects, both as initial therapy and as a switch strategy.

The practical implications of the above data are that EFV should in general be avoided in older people as initial therapy, which is concordant with current treatment guidelines. Similarly, clinicians should strongly consider switching patients on EFV who have neurocognitive complaints to a different regimen – most commonly one based on DTG or BIC, or alternatively an NNRTI with fewer neuropsychiatric side effects (RPV or DOR). For those who have no side effects, a small fraction will realize they actually feel better off EFV – better sleep, less dizziness, sharper mentally – but others will notice no improvement with the switch [81].

Multiple studies have found that neuropsychiatric adverse effects can be seen with INSTIs, with higher rates in DTG compared with RAL or EVG [82–85]. Although neuropsychiatric toxicity with INSTIs is rare and has not been found to be more common relative to comparator drugs, it is still important to keep in mind, given the widespread use of INSTIs and the high prevalence of cognitive impairment in older adults with HIV.

**CARDIOVASCULAR RISK**

People with HIV have higher risk of cardiovascular disease and myocardial infarction compared with those without HIV [86]. This is thought to be a result of both traditional risk factors like diabetes, hyperlipidemia, and smoking [86], and HIV-related inflammation and immune activation [87,88]. Not surprisingly, the risk of cardiovascular disease in people with HIV increases substantially with advancing age [89].

Several antiretroviral agents have been implicated in a potential increase in cardiovascular risk, with some of this effect mediated by more unfavorable lipid profiles. Observational studies have consistently found an association between protease inhibitors and excess risk of cardiovascular events, including the protease inhibitor most commonly used today, darunavir [90*]. The lone exception to this potential adverse effect is atazanavir, which was not implicated in the previously referenced D:A:D study, and furthermore, appeared to be protective in a large observational study from the United States Department of Veterans Affairs [91]. A possible mechanism for this beneficial effect of atazanavir is that the drug induces an increase in unconjugated bilirubin, which is known among people with Gilbert’s syndrome to be associated with a lower risk of myocardial infarction (MI). In further support of these data, a prospective randomized study comparing RAL, DRV/r, and ATV/r demonstrated that of the three, ATV/r had the slowest rate of carotid–intima–media thickness progression [92], and that bilirubin levels appeared to influence this effect. On the basis of these results, if a boosted protease inhibitor is
chosen for inclusion in ART, we would recommend using atazanavir over darunavir in older people with cardiovascular disease, provided the patient does not harbor protease inhibitor-resistant virus.

Multiple studies have shown an association between ABC use and increased risk of cardiovascular disease, in particular MI, compared with other NRTIs [93–96,97*]. Most recently, the NA-ACCORD study found an increased risk of myocardial infarction with recent ABC use after adjustment for known cardiovascular risk factors [97*]. The data are mixed, however, with a pooled analysis of over 13 000 clinical trial participants finding no long-term increase in cardiovascular risk with ABC [98], although the study participants in these trials were young and had relatively low risk for cardiovascular events. The mechanism of increased risk of myocardial infarction with ABC may relate to changes in platelet reactivity [99*]. Given the availability of multiple other ART strategies, as well as the increased cardiovascular risk inherent with aging, we suggest avoiding ABC-containing regimens in older people with HIV unless there are no appropriate alternative options.

WEIGHT GAIN

Obesity rates are rising among people with HIV, and as in the general population, older age has consistently been associated with greater obesity risk [100–102]. A potential association between INSTIs and weight gain was first noted in observational studies of patients switching from non-INSTI-based regimen [103–106]. In several studies, female sex and black race were risk factors [103,105,106]. One study found that the risk of weight gain was higher in younger patients, but another found a higher risk in older patients [103,107].

Multiple RCTs now support the association between INSTIs and weight gain, both as initial therapy and after switching. In one study of ART-naïve participants comparing RAL to ATV/r or DRV/r, there were higher rates of severe weight gain and a greater increase in waist circumference in participants receiving RAL after 24 months of follow-up [108*]. In two RCTs in sub-Saharan Africa comparing DTG to EFV, DTG-containing regimens were associated with increased body weight, trunk fat, and greater rates of clinical obesity after 24 months of follow-up. The effect was particularly strong in women, with weight gain greater in one of the studies when DTG was given in combination with TAF/FTC rather than TDF/FTC [109*]. In a study of mostly older men receiving boosted protease inhibitor-based regimens, switching the boosted protease inhibitor to DTG led to improvement in lipid parameters but significantly greater weight gain than remaining on the original regimen [110]. Finally, a pooled analysis of eight RCTs of treatment-naïve people with HIV found that INSTIs were associated with more weight gain than protease inhibitors or NRTIs, and that DTG and BIC were associated with more weight gain than EVG/c [111*].

Despite this evidence associating weight gain with certain ART regimens, many unknowns remain. Although trunk fat and central adiposity correlate with poorer outcomes in other metabolic diseases, the clinical significance of ART-related weight gain has not yet been characterized. One study demonstrated that switching from TDF to TAF led to a shift in cardiac risk profile because of increased lipids and weight [112*], although it was not sufficiently long to show an actual increase in clinical events. It is also unknown whether weight gain can be reversed by switching from an INSTI to a different drug class, or modifying the TAF/FTC component. Finally, the differential weight gain between TAF-containing regimens compared with those with TDF may be the result of an augmenting effect of TAF, an appetite-suppressive effect of TDF, or both. Because of these uncertainties and the otherwise excellent tolerability, potency, and effectiveness of INSTI and TAF-based regimens, these agents should remain as first-line therapy in most older people with HIV.

KEY RESEARCH QUESTIONS

In light of the current preferred agents for ART and gaps in the literature with respect to toxicity in older people, we consider the following to be the key research questions moving forward:

1. Is INSTI-associated weight gain reversible after switching to a different medication?
2. Does INSTI-associated weight gain translate into clinically meaningful increases in metabolic risk or decreases in quality of life?
3. Does the weight gain and the small increases in lipid levels with TAF relative to TDF translate into clinically meaningful increases in cardiovascular risk?
4. As neurocognitive decline is so common in aging, are there any antiretroviral strategies that influence the process?
5. Should the apparent cardiovascular benefit of atazanavir over darunavir prompt a re-appraisal of this drug in older people with HIV who need protease inhibitor-based therapy?
6. As older adults are at higher risk for ART-associated toxicities, does dual therapy have additional benefit in this population?
CONCLUSION

There are multiple potential toxicities of ART to consider when selecting a regimen for older people. Specific agents or drug classes have been implicated in adverse bone or renal effects, weight gain, neuropsychiatric and neurocognitive effects, and cardiovascular risk. With the ongoing importance of INSTIs as the anchor of preferred ART regimens, further characterization of INSTI-related weight gain is a critically important current research priority in understanding ART toxicity.

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Conflicts of interest
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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

Switching to DTG
Clifford DB, Evans S, Yang Y, nnucleoside reverse transcriptase
Systematic review and meta-analysis:
Orlando G, Meraviglia P, Cordier L, Long-term impact of efavirenz on Mills AM, Cohen C, Dejesus E, CHARTER Group. Long-term efavirenz use is a comparison of neuropsy-
et al.
Brown TT, Moser C, Currier JS, Doravirine/lamivudine/tenofovir dis-
Wolters Kluwer Health, Inc. All rights reserved.

HIV and aging
formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-
52. Munkoz J, Okwera A, Nakasuga N, et al. Influence of efavirenz pharma-
56. Mollan KR, Tiniere C, Hellewee JN, et al. Race/ethnicity and the pharma-
kinecogntics of reported suicidality with efavirenz among clinical trials parti-
60. Large cohort study with extensive longitudinal neuropsychological testing, which found no difference in neurocognitive functioning between patients receiving EFV, those switched off EFV, and those who never received EFV.
64. Cooper DA, Heera J, Heera J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-


Large prospective multicohort study finding association between protease inhibitors and excess risk of cardiovascular events.


Cohort study finding increased risk of myocardial infarction with recent ABC use after adjustment for known cardiovascular risk factors.


Study providing insight into possible mechanism of increased risk of myocardial infarction with ABC being mediated by changes in platelet reactivity.


Randomized control trial of ART-naïve participants finding greater increase in waist circumference if switching to RAL compared with ARV/R or DRV/R.


Study including data from two randomized control trials finding increased weight gain in women receiving DTG and in particular when given in combination with TAF/FTC rather than TDF/FTC.


Pooled analysis of eight RCTs of ART-naïve participants finding that INSTIs associated with greater weight gain than protease inhibitors or NRIs, and that DTG and BIC were associated with more weight gain than ETVG/c.


Observational study finding that switching from TDF to TAF led to a shift in cardiac risk profile because of increased lipids and weight.