CARING FOR THE AGING HIV PATIENT

DR MARLIN J McKAY
GP, Goldman Medical Centre
Florida, Roodepoort
Outline

- Introduction
- Effects of HIV on Aging
- HIV and Comorbidities
- HIV, Polypharmacy and Drug-drug Interactions
- Conclusion and take home points
HIV and aging

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Corresponding Editor: Eskild Petersen, Aarhus, Denmark
REVIEW

EDUCATIONAL OBJECTIVE: Readers will recognize and manage human immunodeficiency virus infection in their older patients

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National Military Medical Center,
Bethesda, MD

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Infectious Diseases Service, MedStar
Washington Hospital Center,
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Care of the aging HIV patient
Review

Understanding mechanisms to promote successful aging in persons living with HIV

Gerome V. Escota*, Jane A. O’Halloran, William G. Powderly, Rachel M. Presti

Division of Infectious Diseases, Washington University School of Medicine, Saint Louis, MO, USA
Life Expectancy in Older HIV-Positive Adults in Modern ART Era

- Population-based cohort study of survival in HIV-infected pts (n = 2440) and uninfected controls matched by age and sex (n = 14,588) in Denmark.
ATHENA: Older Patients Becoming More Prevalent in the HIV-Infected Population

- Observational cohort of 10,278 HIV-infected patients in the Netherlands
- Modeling study projections:
  - Proportion of HIV-positive patients ≥ 50 yrs of age to increase from 28% in 2010 to 73% in 2030
  - Median age of HIV-positive patients on combination ART to increase from 43.9 yrs in 2010 to 56.6 yrs in 2030


Slide credit: clinicaloptions.com
Older HIV-Infected Pts at Increased Risk for Multiple Comorbidities

- AGEhIV: prospective cohort study of HIV-infected pts (n = 540) vs controls (n = 524) 45 yrs of age or older

HIV Pts More Likely to Experience Bone Fractures, CVD, Diabetes, Renal Failure

Interplay of Age with Morbidity

#1: THE PATIENT
- Individual and social factors
- Higher rate of traditional risk factors: smoking, dyslipidemia, HTN, diabetes, obesity

#2: THE VIRUS(ES)
- HIV infection itself
- Inflammation and immune activation
- Coinfections: HCV

Metabolic Complications:
- Cardiovascular Disease
- Renal Disease
- Osteoporosis
- Non-AIDS Cancers

#3: THE TREATMENT
- ART and toxicity

Slide credit: clinicaloptions.com
Cardiovascular Disease

- Cardiovascular disease (CVD) is a leading cause of death in PLWH on effective ART (Rodger et al., 2013).

- Deaths from CVD increased two-fold despite a decrease in CVD-related mortality in the general population (Feinstein et al., 2016).

- Multiple factors have been attributed to the increased CVD risk observed in PLWH, including
  - the HIV infection itself,
  - ART toxicity, and
  - increased rates of traditional risk factors including smoking, T2DM, Hypertension, and Dyslipidaemia (Triant et al., 2007, Saves et al., 2003).
The Link Between HIV and CVD and Age

- Rate of acute MI higher in HIV-positive pts\[1\]
- HIV infection is a risk factor for ischemic stroke\[2\]
- HIV-infected men have a greater prevalence of coronary artery plaques\[1,3\]

The Relationship Between CVD Risk in HIV and HIV Treatment Is U-Shaped

Rapid decrease after starting ART

Moderate increase over time driven by
- Traditional risk factors
- Persistent inflammation
- Drugs?

Slide credit: clinicaloptions.com
CVD Mortality Higher in HIV-Infected Patients, Even With Virologic Suppression

- Analysis of CVD-related mortality in HIV-infected patients in New York City HIV Surveillance Registry 2001-2012 (N = 145,845)
  - 71.5% male; median age: 49 yrs
- From 2001-2012, CVD mortality increased in HIV-infected patients (from 6% to 15%) while decreasing in the general population
- Age-adjusted rate of CVD mortality markedly decreased for HIV-infected patients with virologic suppression
  - HIV-1 RNA ≥ 400 copies/mL: 8.02/1000 PY
  - HIV-1 RNA < 400 copies/mL: 3.99/1000 PY
  - General population: 3.22/1000 PY

## Studies Addressing Abacavir and MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Association?</th>
<th>Description</th>
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<tr>
<td>D:A:D[1]</td>
<td>✓</td>
<td>Cohort collaboration (prospective)</td>
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<tr>
<td>Danish HIV Cohort[2]</td>
<td>✓</td>
<td>Cohort (linked with registries)</td>
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<td>Montreal study[3]</td>
<td>✓</td>
<td>Nested case-control study</td>
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<tr>
<td>SMART[4]</td>
<td>✓</td>
<td>Post hoc subgroup analysis of RCT (use of ABC not randomised)</td>
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<tr>
<td>Desai et al[6]</td>
<td>✓</td>
<td>Cohort (retrospective)</td>
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<tr>
<td>Swiss HIV Cohort[7]</td>
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<td>Cohort (prospective)</td>
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<tr>
<td>FHDH ANRS CO4[8]</td>
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<td>Nested case-control study</td>
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<td>NA-ACCORD[9]</td>
<td>?</td>
<td>Cohort (retrospective)</td>
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<tr>
<td>VA Clinical Case Registry[10]</td>
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<td>Cohort (retrospective)</td>
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<tr>
<td>Brothers et al. analysis[11]</td>
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<td>Post hoc meta-analysis of RCTs</td>
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<tr>
<td>ACTG A5001/ALLRT[12]</td>
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<td>Post hoc meta-analysis of RCTs</td>
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<tr>
<td>FDA meta-analysis[13]</td>
<td>✗</td>
<td>Post hoc meta-analysis of RCTs</td>
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Interventions Contributing to Reductions in CVD in HIV-Infected Pts

- Modeling study using data from 8791 pts in ATHENA study

![Reductions in CVD by Intervention](image)


Slide credit: clinicaloptions.com
# Drug–Drug Interactions With ART and CVD and Antihypertensive Therapy

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<tr>
<th>Antiretroviral</th>
<th>Contraindicated</th>
<th>Titrate Dose</th>
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<tr>
<td>ARV/RTV or DRV/RTV</td>
<td>Lercanidipine Dabigatran*</td>
<td>Amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamil, indapamide, doxazosin, amlodipine, diltiazem, verapamil, warfarin</td>
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<tr>
<td>EFV</td>
<td>Lercanidipine, amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamil, indapamide, doxazosin</td>
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<tr>
<td>EVG/COBI</td>
<td>Lercanidipine Dabigatran*</td>
<td>Amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamil, indapamide, doxazosin, amlodipine, diltiazem, verapamil, warfarin</td>
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</tbody>
</table>

DTG, RAL, ABC, FTC, 3TC, and TDF have no significant interactions.
*If CrCl < 50 mL/min.

Statins Decrease Immune Activation and Aortic Plaque in Treated HIV Infection

- REPRIEVE: double-blind, randomized phase IV trial of pitavastatin (planned N = 6500) now enrolling


Slide credit: clinicaloptions.com
Approach to Lipid-Lowering (Statin) Therapy

- HIV-infected patients are at increased risk for ASCVD\textsuperscript{[1,2]}
  - ART can cause increases in triglycerides and TC, VLDL, LDL, and HDL
- Prescribing statins can be challenging due to DDIs, insulin resistance, adverse events, and increased pill burden\textsuperscript{[1]}

<table>
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<tr>
<th>Statin Therapy</th>
<th>Recommendation</th>
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<tr>
<td>Goal of therapy</td>
<td>CVD risk reduction\textsuperscript{[1]}</td>
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<tr>
<td>Screening</td>
<td>A fasting lipid panel should be obtained in all newly diagnosed HIV-infected patients\textsuperscript{[1,3]}</td>
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<td></td>
<td>Lipid screening annually\textsuperscript{[3]}</td>
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<tr>
<td>Treatment</td>
<td>Statin therapy is first-line therapy for elevated LDL and non-HDL\textsuperscript{[1]}</td>
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<td>Moderate- or high-intensity statin therapy should be considered, with proper dosing according to specific statin and anticipated DDIs with ART\textsuperscript{[1]}</td>
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<td></td>
<td>Lifestyle therapy is the recommended first step\textsuperscript{[4]}</td>
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<tr>
<td>Other</td>
<td>Patient–provider discussion is central to decisions on drug treatment\textsuperscript{[1]}</td>
</tr>
</tbody>
</table>

References in slidenotes.
## Statin Dosing in the Setting of ART

### PI- or COBI-Containing Regimens

<table>
<thead>
<tr>
<th>High-Intensity Statin</th>
<th>Moderate-Intensity Statin</th>
<th>Low-Intensity Statin</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin 20 mg</td>
<td>Atorvastatin 10 mg</td>
<td>Pravastatin 10-20 mg</td>
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<td>Rosuvastatin 10-20 mg</td>
<td>Rosuvastatin 5 mg</td>
<td>Fluvastatin 20-40 mg</td>
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<tr>
<td>Pravastatin 40-80 mg*</td>
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<td>Pitavastatin 1 mg</td>
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<tr>
<td>Pitavastatin 2-4 mg</td>
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</tbody>
</table>

*Simvastatin and lovastatin are contraindicated for pts receiving a PI or COBI*

*With darunavir, reduce pravastatin to 20-40 mg*

### NNRTI-, RAL-, or DTG-Containing Regimens

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<th>High-Intensity Statin</th>
<th>Moderate-Intensity Statin</th>
<th>Low-Intensity Statin</th>
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</thead>
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<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 mg</td>
<td>Rosuvastatin 10 mg</td>
<td>Fluvastatin 20-40 mg</td>
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<tr>
<td>Pravastatin 40-80 mg</td>
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<td>Pitavastatin 1 mg</td>
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<tr>
<td>Pitavastatin 2-4 mg</td>
<td></td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td></td>
<td>Simvastatin 10 mg</td>
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<tr>
<td>Simvastatin 20-40 mg</td>
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</tbody>
</table>

All doses daily.

Take-home Points

- Treat HIV promptly
- Select a regimen that will be well tolerated and not aggravate underlying conditions or increase CVD risk
- Beware of drug–drug interactions, e.g. between CCB’s and ART components
- Do not hesitate in addressing CVD risk and consider statins as indicated
MACS: Rates of DM Increased in HIV-Positive Pts on ART

- Rate of incident DM was 4.7 cases/100 PYs in HIV-positive men vs 1.4 cases/100 PYs in seronegative men

Fracture Prevalence Is Increased in Older HIV-Positive Pts

- 8525 HIV-infected pts compared with 2,208,792 uninfected pts in Partners HealthCare System

Recommendations for Evaluation and Management of Bone Disease in HIV

- DXA should be performed
  - Men ≥ 50 yrs of age
  - Postmenopausal women
  - People with a history of fragility fracture
  - Patients receiving chronic glucocorticoid treatment
  - People at high risk for falls

- If low bone mineral density is detected:
  - Assess for secondary causes (eg, vitamin D deficiency, hypothyroid, hypogonadism)
  - Calcium and vitamin D supplementation
  - Bisphosphonate may be indicated if osteoporosis detected
  - Avoidance of TDF

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Risk (standardized incidence ratio)</th>
<th>Screening recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>33.4–42.9</td>
<td>European AIDS Clinical Society: Consider digital rectal examination with or without a Papanicolaou smear every 1–3 years*</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>14.7–31.7</td>
<td>None</td>
</tr>
<tr>
<td>Liver</td>
<td>7.0–7.7</td>
<td>European AIDS Clinical Society: Ultrasonography, alpha fetoprotein every 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>National Cancer Institute: No recommendation</td>
</tr>
<tr>
<td>Squamous cell carcinoma, basal cell carcinoma</td>
<td>3.2</td>
<td>European AIDS Clinical Society, National Cancer Institute: Consider routine whole-body skin examinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US Preventive Services Task Force: Insufficient evidence</td>
</tr>
<tr>
<td>Lung</td>
<td>2.2–6.6</td>
<td>American Cancer Society: Consider chest radiography in high-risk patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>National Cancer Institute, US Preventive Services Task Force: Consider low-dose computed tomography in high-risk patients</td>
</tr>
</tbody>
</table>

*Specific to HIV-infected men who have sex with men; currently no national guidelines.

*High-risk patients include those ages 55 to 74 in fairly good health who have a smoking history ≥ 30 pack-years AND are still smoking or have quit within the last 15 years.

Derived from Shiels et al, Deeken et al, Powles et al, and Patel et al.
### HIV and HAND

- HIV-associated neurocognitive disorders are common, with an estimated 50% of HIV-infected patients experiencing some degree of cognitive loss and some progressing to dementia.

- Can occur despite good HIV control with cART.

- Presentation: fluctuating symptoms such as psychomotor retardation, difficulty multitasking, and apathy.

- MMSE should not be used to screen – use Montreal Cognitive Assessment has been suggested as the best screening instrument in elderly HIV-infected patients; it is available at no cost at [www.mocatest.org](http://www.mocatest.org).

- Diagnosis of exclusion
# DHHS: Considerations for Initial ART Based on Age-Related Comorbidity

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Consider Avoiding</th>
<th>Options for Consideration*</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD (eGFR &lt; 60 mL/min)</td>
<td>▪ TDF, especially in RTV-containing regimens</td>
<td>▪ FTC/TAF</td>
<td>▪ If eGFR &gt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>▪ ABC/3TC</td>
<td>▪ ABC/3TC</td>
<td>▪ If HLA-B*5701 negative; 3TC requires dose adjustment if CrCl &lt; 50 mL/min</td>
</tr>
<tr>
<td></td>
<td>▪ DRV/RTV + RAL</td>
<td>▪ DRV/RTV + RAL</td>
<td>▪ If TAF or ABC cannot be used; if HIV-1 RNA &lt; 100,000 copies/mL and CD4+ cell count &gt; 200 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>▪ LPV/RTV + 3TC</td>
<td>▪ LPV/RTV + 3TC</td>
<td>▪ If TAF or ABC cannot be used; 3TC dose adjustment if CrCl &lt; 50 mL/min</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>▪ TDF</td>
<td>▪ FTC/TAF</td>
<td>▪ If HLA-B*5701 negative</td>
</tr>
<tr>
<td></td>
<td>▪ ABC/3TC</td>
<td>▪ ABC/3TC</td>
<td></td>
</tr>
<tr>
<td>CVD risk</td>
<td>▪ ABC</td>
<td>▪ DTG-, RAL-, or RPV-based regimens</td>
<td>▪ If choosing boosted PI, ATV may be preferable to DRV, but further study needed</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>▪ PI/RTV or PI/COBI</td>
<td>▪ DTG-, RAL-, or RPV-based regimens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ EVG/COBI</td>
<td>▪ TDF associated with lower lipid levels vs ABC or TAF</td>
<td></td>
</tr>
</tbody>
</table>

*This section of the guidelines has not yet been updated to reflect February 2018 FDA approval of BIC/FTC/TAF.*

DHHS Guidelines. May 2018. Slide credit: clinicaloptions.com
Polypharmacy
Comorbidities & polypharmacy in uninfected versus infected elderly

- **GEPPO Cohort** (prospective multicentric italian cohort including > 65 years old individuals)
- **1258 HIV positive** (65-74 y: 965; > 75 y: 292) and **315 HIV negative** (224 and 91)

### Prevalence of comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>HIV neg</th>
<th>&lt;10 HIV duration</th>
<th>10-20 HIV duration</th>
<th>≥20 HIV duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
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<tr>
<td>COPD</td>
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<tr>
<td>Chronic kidney disease</td>
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<tr>
<td>Cardiovascular disease</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypertension</td>
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</table>

### Polypharmacy (> 5 comeds)

- **Overall, prevalence of comorbidities was comparable among HIV infected/uninfected elderly (64%/59%).**
- After stratification based on HIV infection duration, individual comorbidities dyslipidemia, chronic kidney disease, diabetes were more prevalent in infected compared to uninfected individuals.
- **Overall, prevalence of polypharmacy was higher among HIV infected/uninfected elderly (37%/24%).**

Guaraldi G et al. BMC Geriatrics 2018
Consequences of polypharmacy

Polypharmacy: ≥ 5 medications

Nonadherence
- Possible causes:
  - Side effects
  - High pill burden
  - Complex dosing regimens
  - Depression
  - Neurocognitive impairment
  - Size of tablets
  - Limited health literacy (misunderstanding of instructions)
  - Health beliefs (being unconvinced about necessity of medication)

Adverse drug reactions
- Most common drug classes associated with ADR in elderly:
  - Cardiovascular drugs
  - Diuretics
  - Anticoagulants
  - NSAIDs
  - Antidiabetics

Geriatric syndromes
- Falls
- Cognitive decline
- Orthostatic hypotension

Drug-drug interactions

Summary

- Polypharmacy \( \uparrow \) risk of DDIs, drug related side effects and medications errors

- Elderly particularly at risk due to \( \uparrow \) age related co-morbidities and age related physiological changes which impact the risk-benefit ratio of many drugs

- For an appropriate management of polypharmacy:
  
  o medication reconciliation
  o review prescriptions
    - indication \( \Rightarrow \) stop unnecessary treatments
    - dose (e.g. adapt to renal function)
    - duration of treatment
    - drug-drug and drug-diseases interactions
    - inappropriate drugs
    - missing medication
  o prioritize medications according to risk and benefit for an individual patient and considering patient preferences
Drug-Drug Interactions
ART Considerations for Pts With Polypharmacy Complications

- Older pts often have multiple comorbidities requiring co-medication
- This requires careful consideration of DDIs, dosing, and potential adherence challenges
- Use of Internet-based tools that are currently updated is highly recommended (eg, HIV iCHART)
- Of the current available third drugs, RAL and DTG have the better interaction profile
Liverpool HIV iChart

Providing summary data of HIV drug interactions.
Full details available at www.hiv-druginteractions.org

Search For Drug Interactions

Sponsors  Privacy  Disclaimer
## Additional Drug–Drug Interactions With ART

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATV/RTV</th>
<th>DRV/RTV</th>
<th>EFV</th>
<th>RPV</th>
<th>DTG</th>
<th>EVG/COBI</th>
<th>RAL</th>
<th>ABC</th>
<th>FTC</th>
<th>3TC</th>
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- ![Green](#): No clinically significant interaction expected
- ![Orange](#): These drugs should not be coadministered
- ![Yellow](#): Potential interaction that may require a dosage adjustment
- ![LightGreen](#): Potential interaction predicted to be of weak intensity

Can we get our patients to age successfully?
Successful aging and the epidemiology of HIV

Figure 1 Factors of and obstacles to successful aging with HIV.
Figure 1
Things to Think About Before Starting Therapy in an Older Patient

- ART recommended for all patients regardless of CD4+ cell count; especially important for older patients
- Adverse drug events from ART and concomitant drugs may occur more frequently in older patients with HIV
  - Bone, kidney, metabolic, cardiovascular, and liver health should be monitored closely
- Polypharmacy is common in older patients with HIV
  - Greater risk of drug–drug interactions
- HIV experts should collaborate with primary care providers and other specialists to optimize medical care of older HIV-infected patients with complex comorbidities
Keeping Healthy HIV Patients Healthy: How to Beat Inflammation and Limit Comorbidities

- Adhere to HIV medications
- Quit smoking
- Refine diet and maintain normal weight
  - For obese individuals, hypocaloric diet can reduce inflammation[1]
- Exercise
  - Study of sedentary HIV-infected patients on ART (N = 49) found that 60 mins brisk walking ± 30 mins strength training 3 times/wk for 12 wks improved functional status and reduced inflammatory markers/immune activation[2]
- Reduce alcohol intake; avoid drugs
- Provide hepatitis and HPV vaccinations
- Advise sunscreen and avoidance of sun overexposure
- Screening:
  - Yearly cervical and anal Pap tests as indicated[3]
  - Colon cancer screening at age 50[3]
  - Breast cancer screening every other yr at age 50[4,5]
  - Prostate screening risks and benefits discussed at age 50[4,6]
  - If HBV+ or HCV+, screen for liver cancer[3]

4. NCI. HIV infection and cancer risk.

Slide credit: clinicaloptions.com
Achieving the fourth 90: healthy aging for people living with HIV

Tiffany G. Harris, Miriam Rabkin and Wafaa M. El-Sadr

AIDS 2018, 32:1563–1569

Keywords: aging, chronic disease, comorbidity, frailty, HIV, multimorbidity, social support