CARING FOR THE AGING HIV PATIENT

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Outline

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

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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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Care of the aging HIV patient

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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

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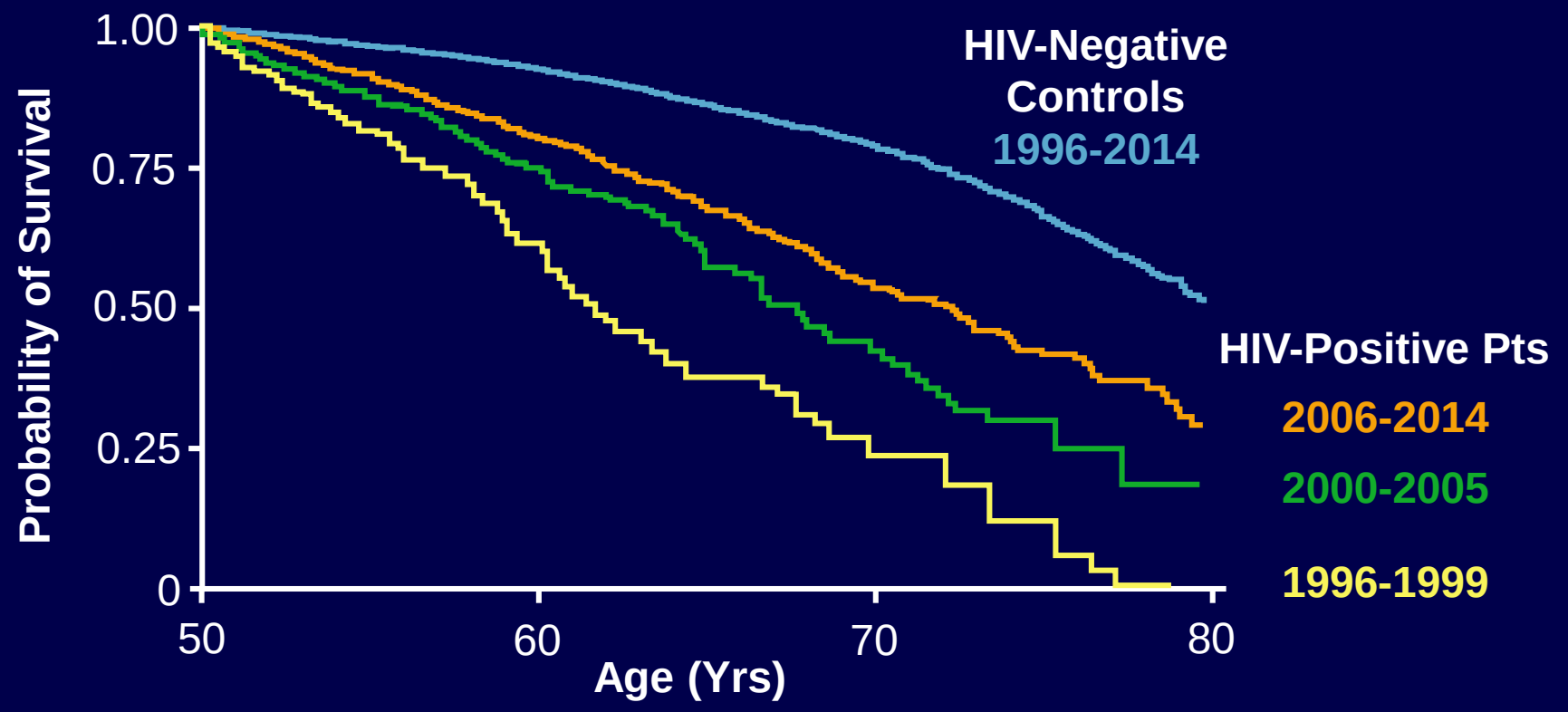
Life Expectancy in Older HIV-Positive Adults in Modern ART Era

- 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

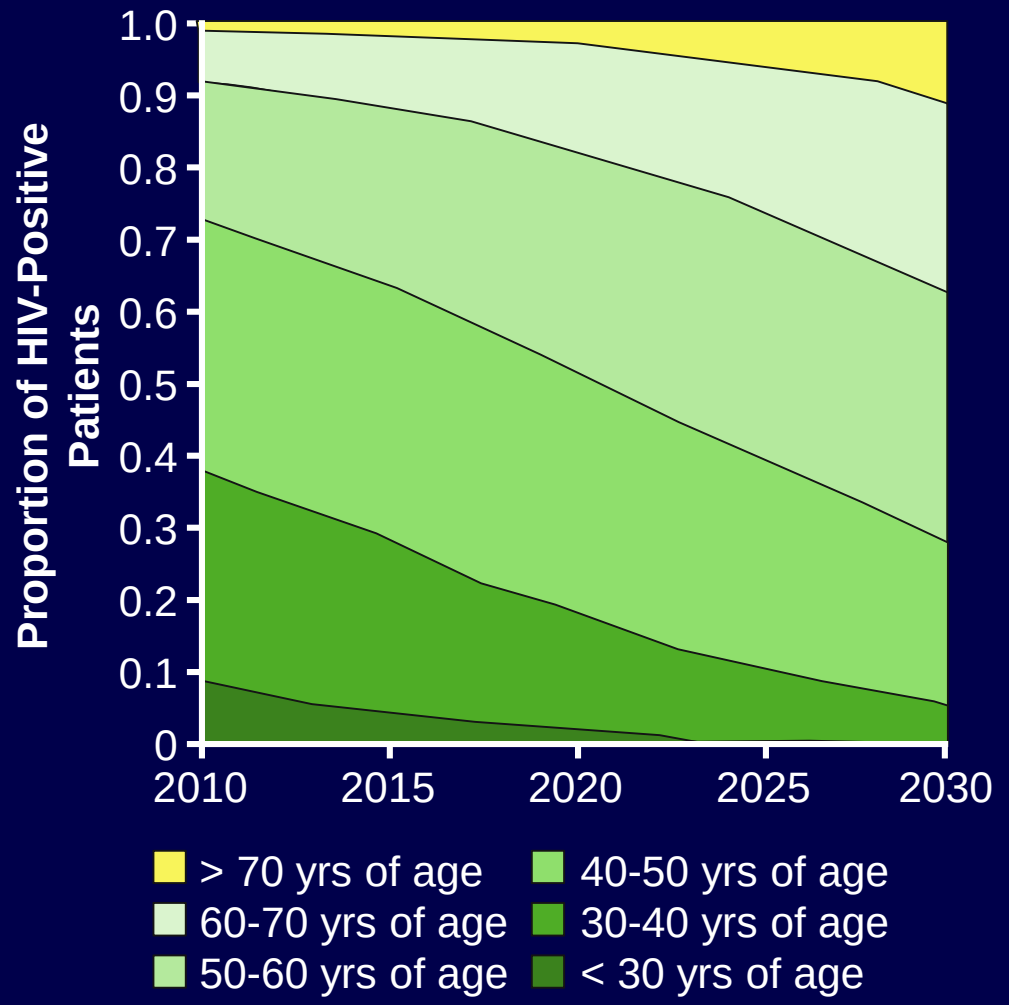


Legarth RA, et al. J Acquir Immune Defic Syndr. 2016;71:213-218.

Slide credit: clinicaloptions.com

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

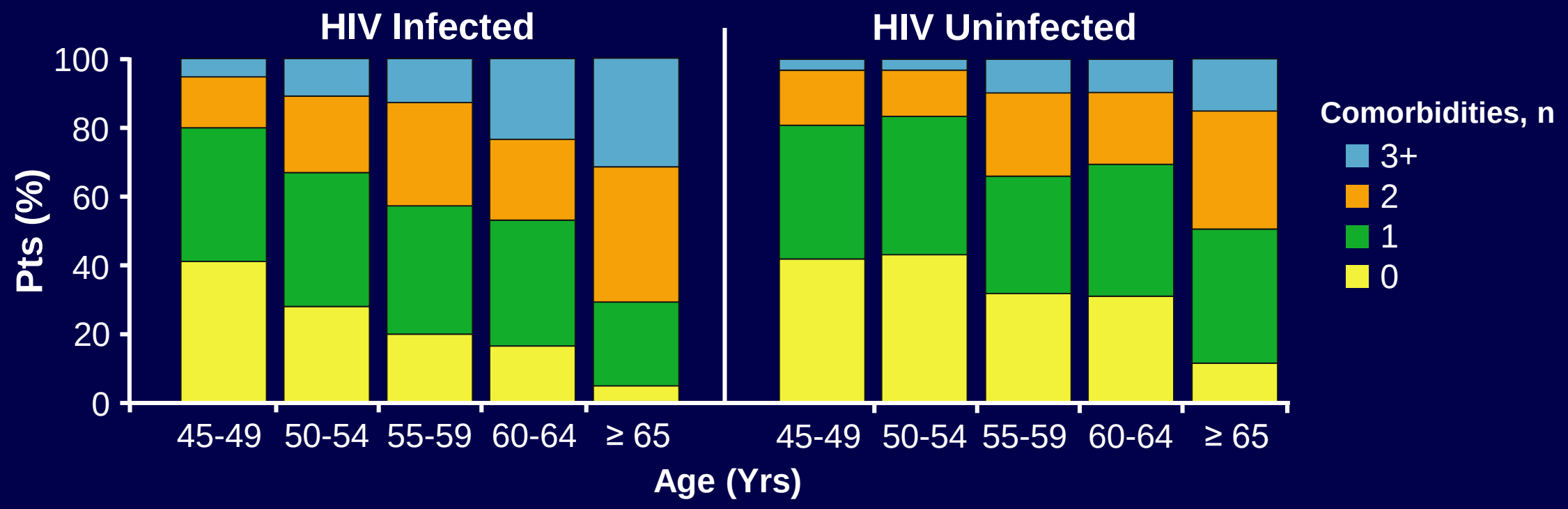


Smit M, et al. Lancet Infect Dis. 2015;15:810-818.

Slide credit: clinicaloptions.com

Older HIV-Infected Pts at Increased Risk for Multiple Comorbidities

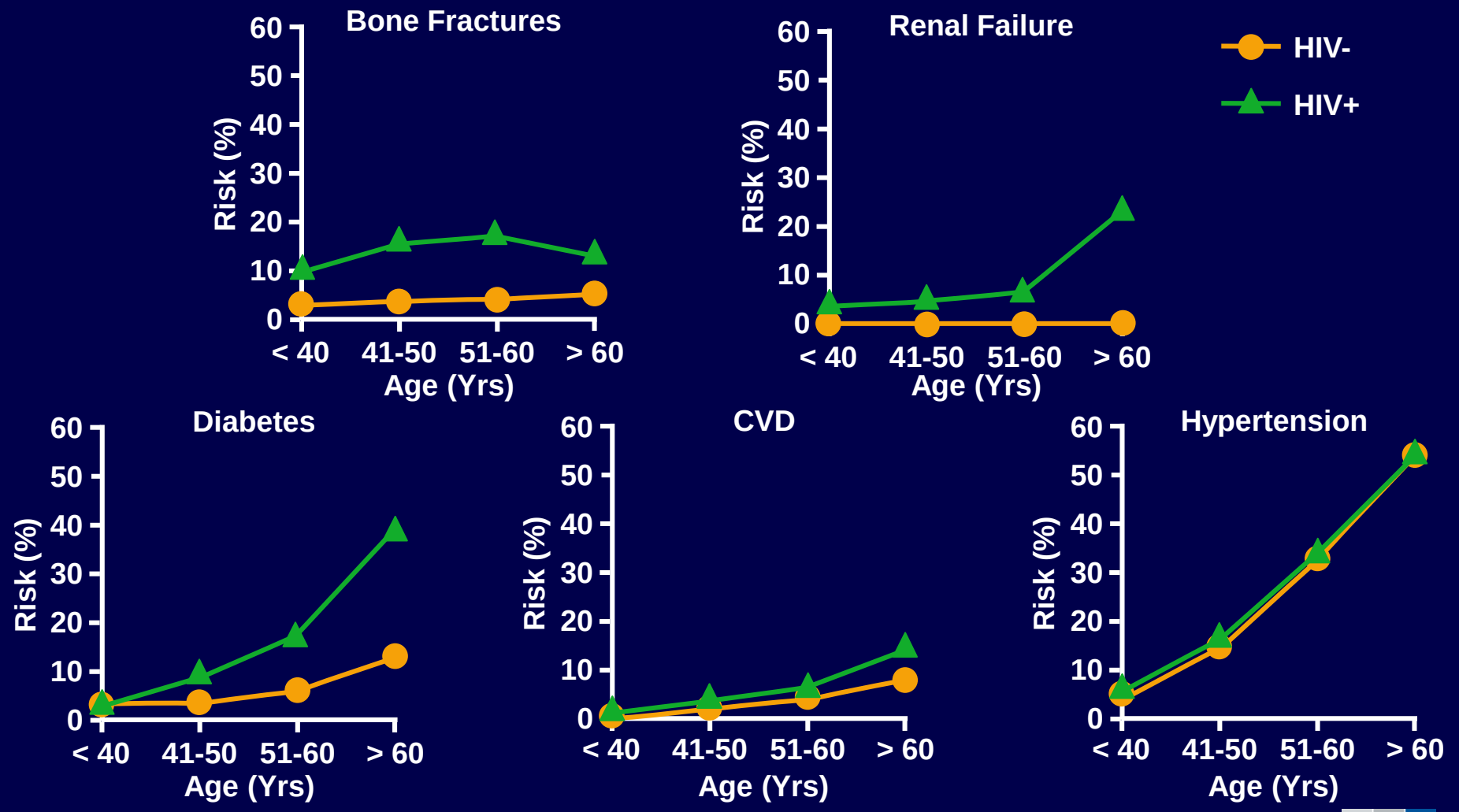
- AGEhIV: prospective cohort study of HIV-infected pts (n = 540) vs controls (n = 524) 45 yrs of age or older



Schouten J, et al. Clin Infect Dis. 2014;59:1787-1797.

Slide credit: clinicaloptions.com

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



Guaraldi G, et al. Clinicoecon Outcomes Res. 2013;5:481-488.

Slide credit: clinicaloptions.com

Interplay of Age with Morbidity

#1: THE PATIENT

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

Metabolic Complications:

Cardiovascular Disease

Renal Disease

Osteoporosis

Non-AIDS Cancers

#2: THE VIRUS(ES)

- HIV infection itself
- Inflammation and immune activation
- Coinfections: HCV

#3: THE TREATMENT

- ART and toxicity

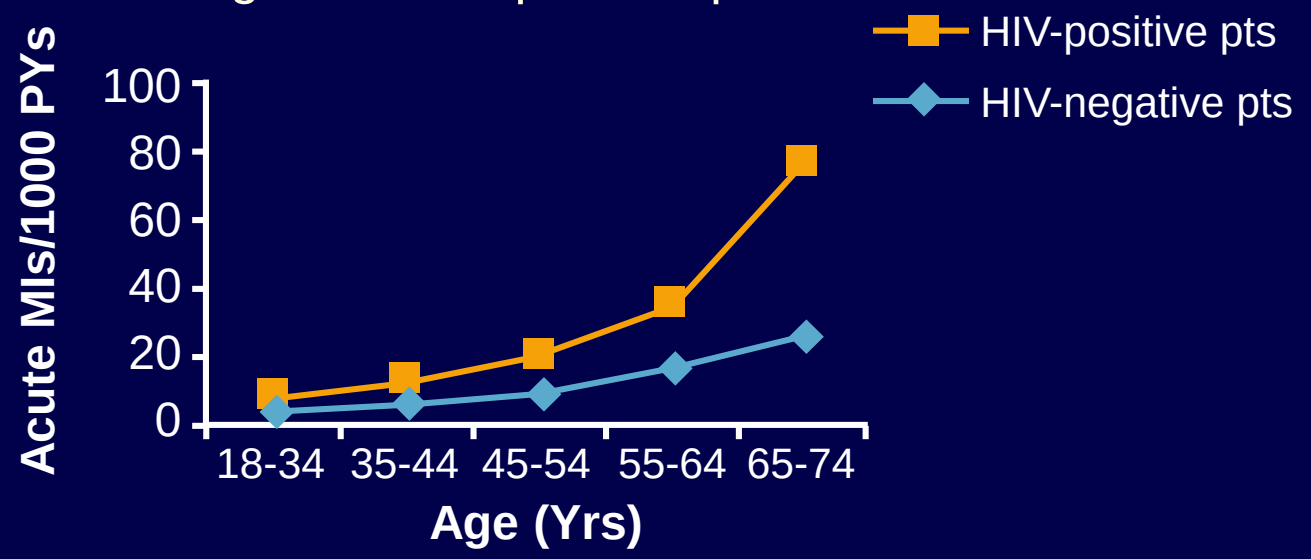
Slide credit: clinicaloptions.com

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

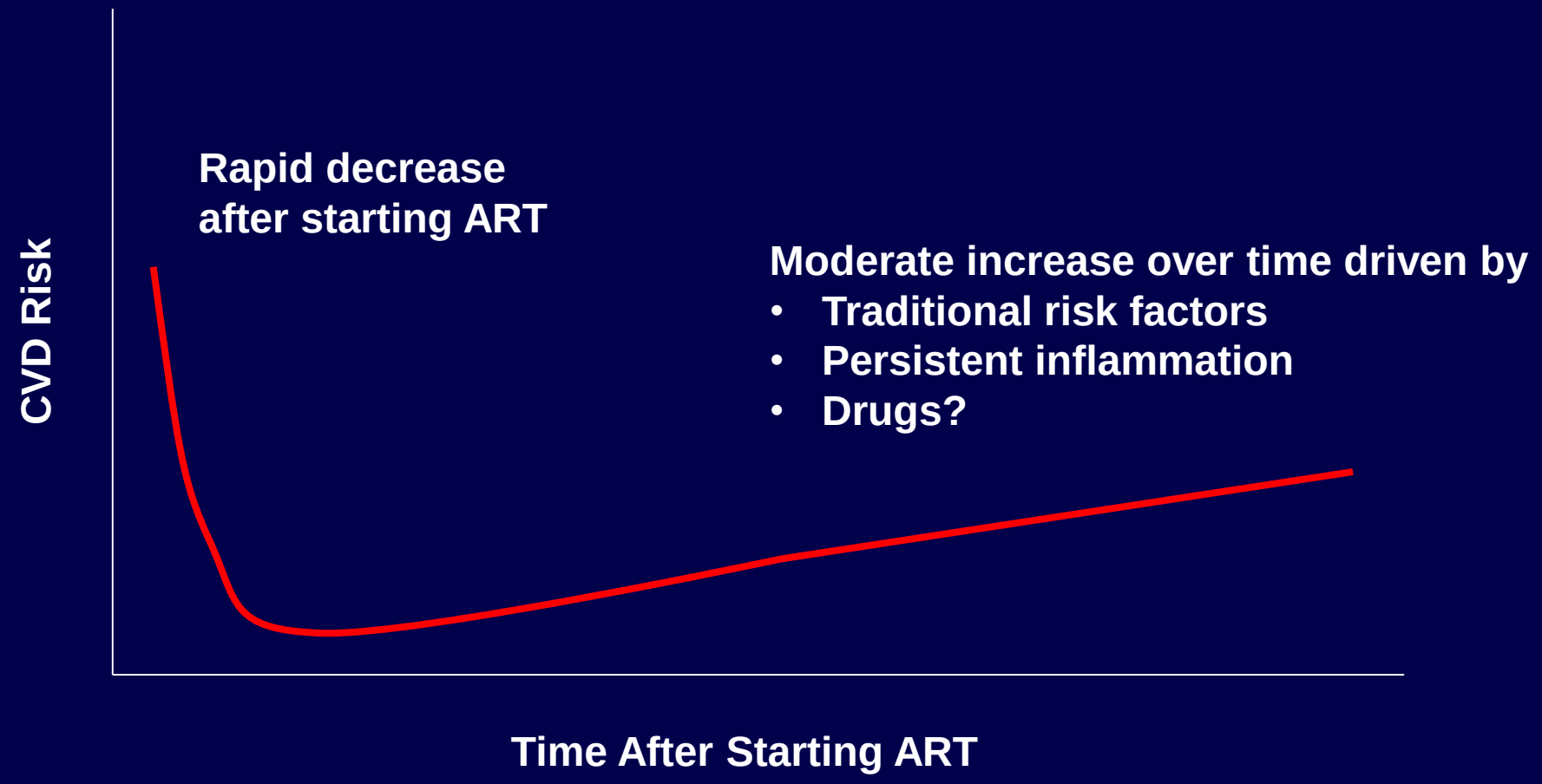
- Rate of acute MI higher in HIV-positive pts[1]



- HIV infection is a risk factor for ischemic stroke[2]
- HIV-infected men have a greater prevalence of coronary artery plaques[1,3]

1. Triant VA, et al. J Clin Endocrinol Metab. 2007;92:2506-2512. 2. Chow FC, et al. J Acquir Immune Defic Syndr. 2012;60:351-358. 3. Post WS, et al. Ann Intern Med. 2014;160:458-467.

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



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

Hanna DB, et al. Clin Infect Dis. 2016;63:1122-1129.

Slide credit: clinicaloptions.com

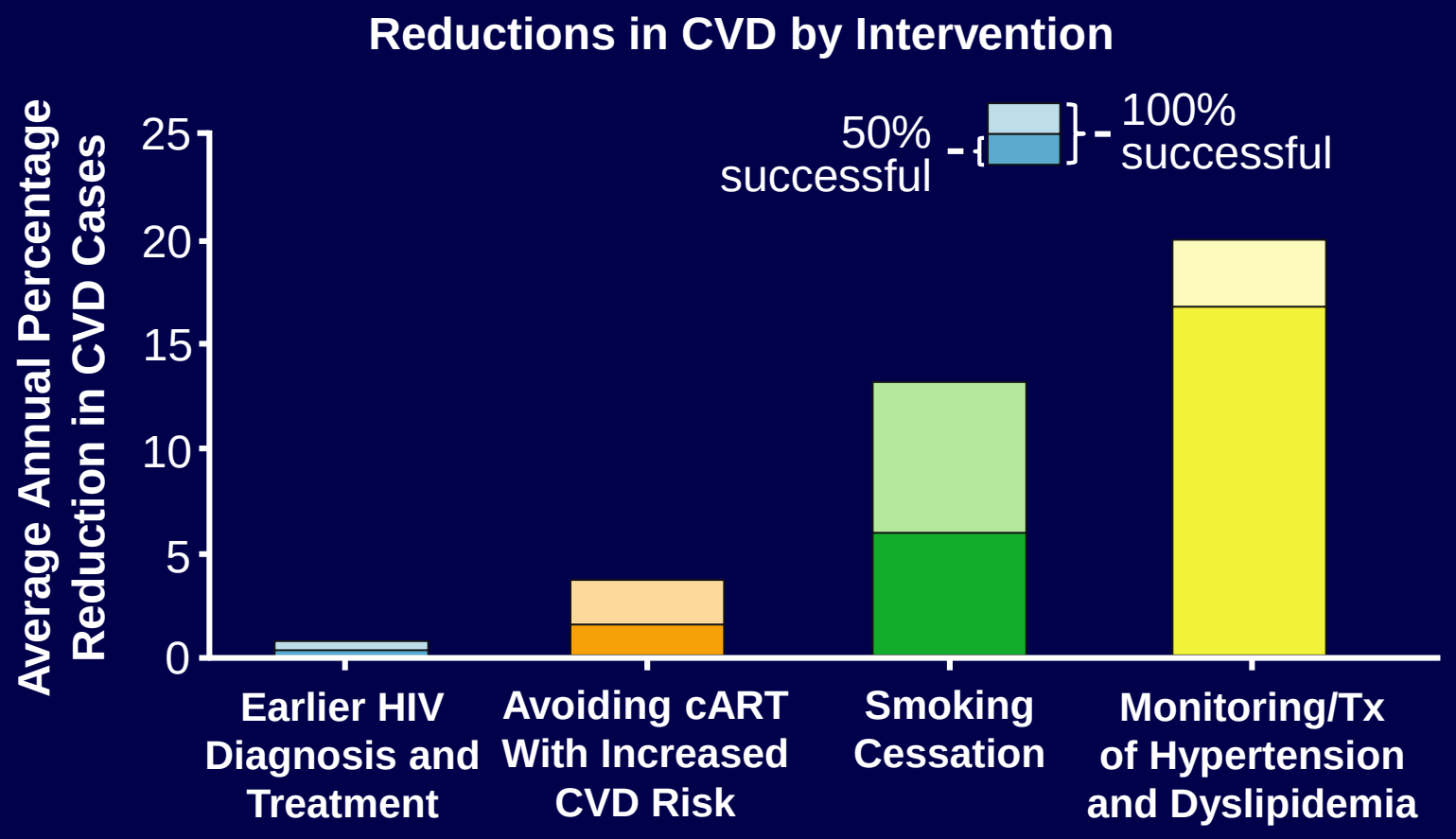
Studies Addressing Abacavir and MI

Study	Association?	Description
D:A:D[1]	✓	Cohort collaboration (prospective)
Danish HIV Cohort[2]	✓	Cohort (linked with registries)
Montreal study[3]	✓	Nested case-control study
SMART[4]	✓	Post hoc subgroup analysis of RCT (use of ABC not randomised)
STEAL[5]	✓	Preplanned secondary analysis of RCT (use of ABC randomised)
Desai et al[6]	✓	Cohort (retrospective)
Swiss HIV Cohort[7]	✓	Cohort (prospective)
FHDH ANRS CO4[8]	?	Nested case-control study
NA-ACCORD[9]	?	Cohort (retrospective)
VA Clinical Case Registry[10]	✗	Cohort (retrospective)
Brothers et al. analysis[11]	✗	Post hoc meta-analysis of RCTs
ACTG A5001/ALLRT[12]	✗	Post hoc meta-analysis of RCTs
FDA meta-analysis[13]	✗	Post hoc meta-analysis of RCTs

1. Friis-Møller N, et al. N Engl J Med. 2003;349:1993-2003. 2. Obel N, et al. HIV Med. 2010;11:130-136. 3. Durand M, et al. J Acquir Immune Defic Syndr. 2011;57:245-253. 4. Phillips AN, et al. Antiv Ther. 2008;13:177-187. 5. Martin A, et al. AIDS. 2010;24:2657-2663. 6. Desai M, et al. Clin Infect Dis. 2015;[Epub ahead of print]. 7. Young J, et al. J Acquir Immune Defic Syndr. 2015;[Epub ahead of print]. 8. Lang S, et al. AIDS. 2010;24:1228-1230. 9. Palella F, et al. CROI 2015. Abstract 749LB. 10. Bedimo RJ, et al. Clin Infect Dis. 2011;53:84-91. 11. Brothers CH, et al. J Acquir Immune Defic Syndr. 2009;51:20-28. 12. Ribaudo HJ, et al. Clin Infect Dis. 2011;52:929-940. 13. Ding X, et al. J Acquir Immune Defic Syndr. 2012;61:441-447.

Interventions Contributing to Reductions in CVD in HIV-Infected Pts

- Modeling study using data from 8791 pts in ATHENA study



van Zoest R, et al. CROI 2017. Abstract 129.

Slide credit: clinicaloptions.com

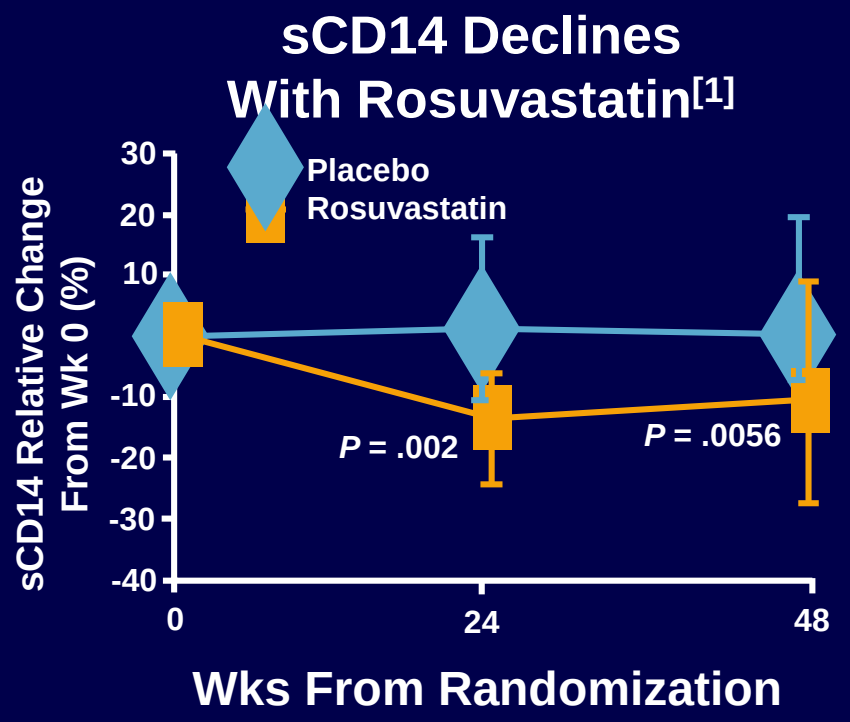
Drug–Drug Interactions With ART and CVD and Antihypertensive Therapy

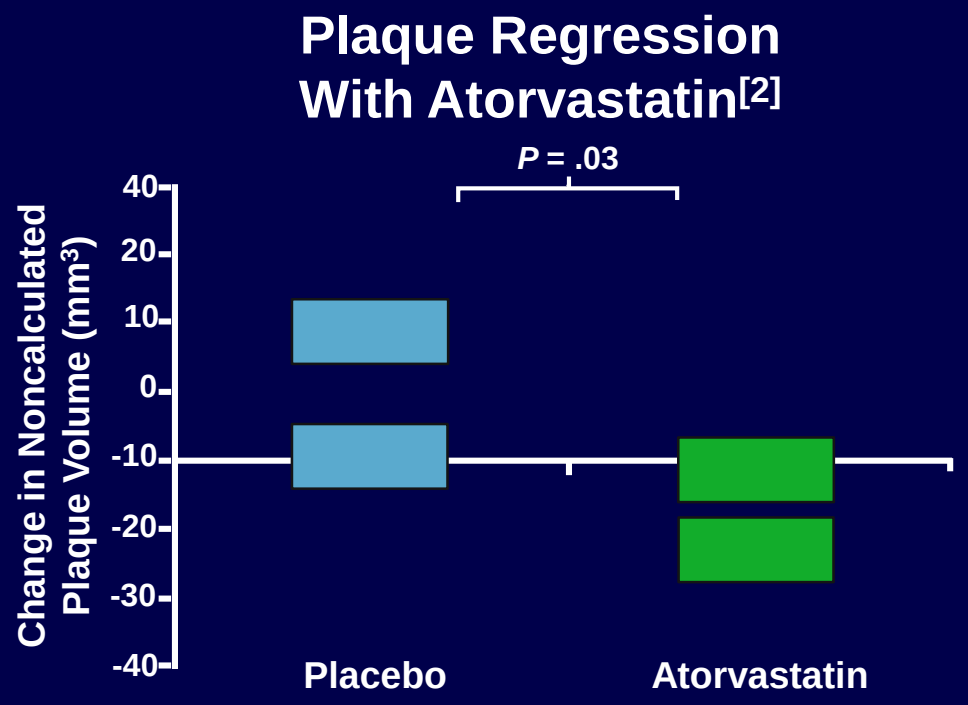
Antiretroviral	Contraindicated	Titrate Dose
ARV/RTV or DRV/RTV	Lercanidipine Dabigatran*	Amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamilo, indapamide, doxazosin, amlodipine, diltiazem, verapamil, warfarin
EFV		Lercanidipine, amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamilo, indapamide, doxazosin
EVG/COBI	Lercanidipine Dabigatran*	Amlodipine, diltiazem, felodipine, lacidipine, nicardipine, nifedipine, nisoldipine, verapamilo, indapamide, doxazosin, amlodipine, diltiazem, verapamil, warfarin

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

DHHS Guidelines. April 2015. EACS Guidelines v. 7.1 November 2014. Dolutegravir [package insert].

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[3]

1. Funderburg NT, et al. J Acquir Immune Defic Syndr. 2015;68:396-404.
2. Lo J, et al. Lancet HIV. 2015;2:e52-e63.
3. ClinicalTrials.gov. NCT02344290.

Slide credit: clinicaloptions.com

Approach to Lipid-Lowering (Statin) Therapy

- HIV-infected patients are at increased risk for ASCVD[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[1]

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

References in slidenotes.

Slide credit: clinicaloptions.com

Statin Dosing in the Setting of ART

PI- or COBI-Containing Regimens		
High-Intensity Statin	**Moderate-Intensity Statin**	**Low-Intensity Statin**
Atorvastatin 20 mg	Atorvastatin 10 mg	Pravastatin 10-20 mg
Rosuvastatin 10-20 mg	Rosuvastatin 5 mg	Fluvastatin 20-40 mg
	Pravastatin 40-80 mg*	Pitavastatin 1 mg
	Pitavastatin 2-4 mg	
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		
High-Intensity Statin	**Moderate-Intensity Statin**	**Low-Intensity Statin**
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Pravastatin 10-20 mg
Rosuvastatin 20 mg	Rosuvastatin 10 mg	Fluvastatin 20-40 mg
	Pravastatin 40-80 mg	Pitavastatin 1 mg
	Pitavastatin 2-4 mg	Lovastatin 20 mg
	Lovastatin 40 mg	Simvastatin 10 mg
	Simvastatin 20-40 mg	

All doses daily.

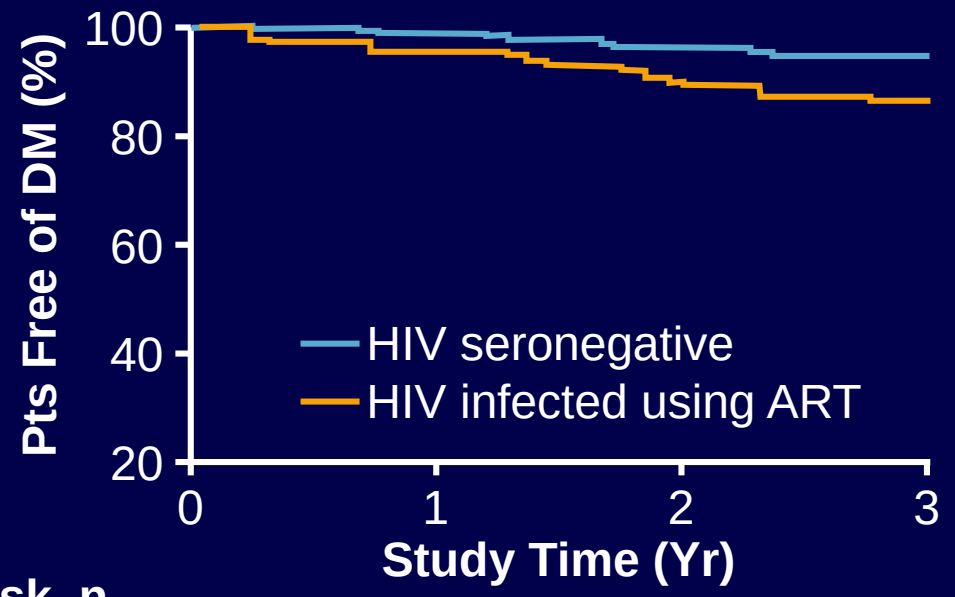
Dubé MP. Lipid management. 2015. p. 241-255.

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

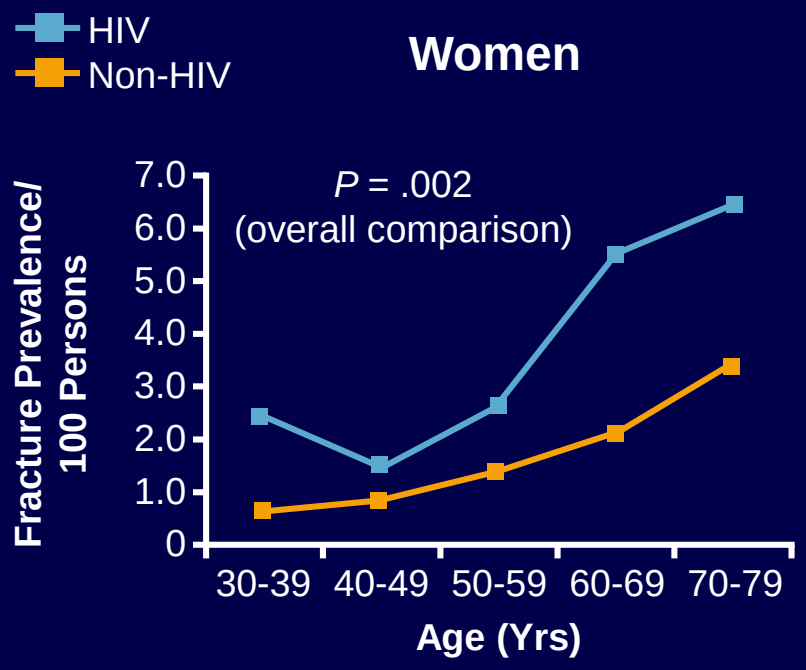


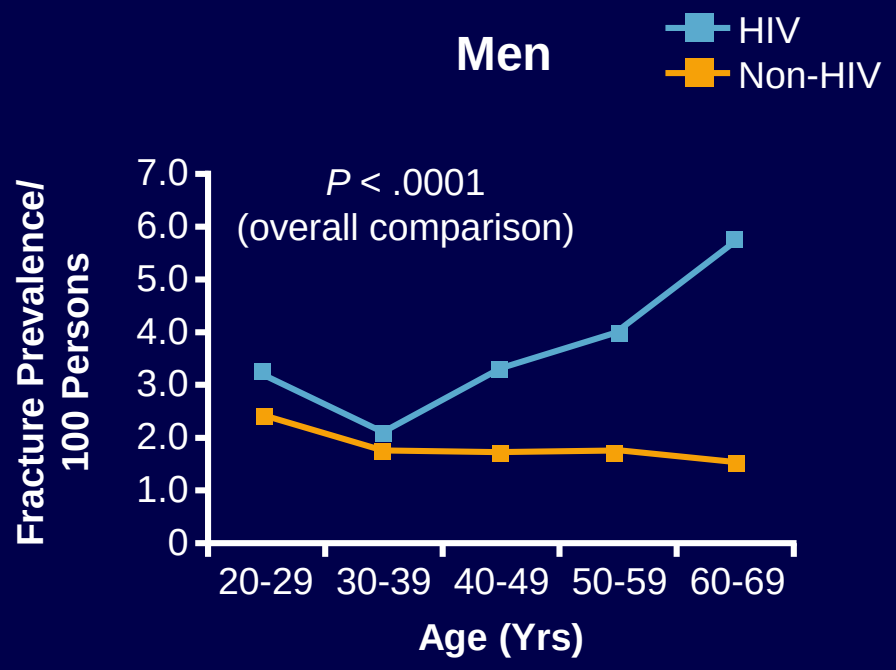
Pts at Risk, n				
HIV seronegative	361	265	177	89
HIV infected using ART	229	204	145	62

Brown TT, et al. Arch Intern Med. 2005;165:1179-1184.

Fracture Prevalence Is Increased in Older HIV-Positive Pts

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





Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504.

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

Brown TT, et al. Clin Infect Dis. 2015;60:1242-1251.

Slide credit: clinicaloptions.com

TABLE 2

Non–AIDS-defining cancers in HIV-infected patients

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

[a]Specific to HIV-infected men who have sex with men; currently no national guidelines.
[b]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,[65] Deeken et al,[66] Powles et al,[67] and Patel et al.[68]

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.
- Diagnosis of exclusion

DHHS: Considerations for Initial ART Based on Age-Related Comorbidity

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

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

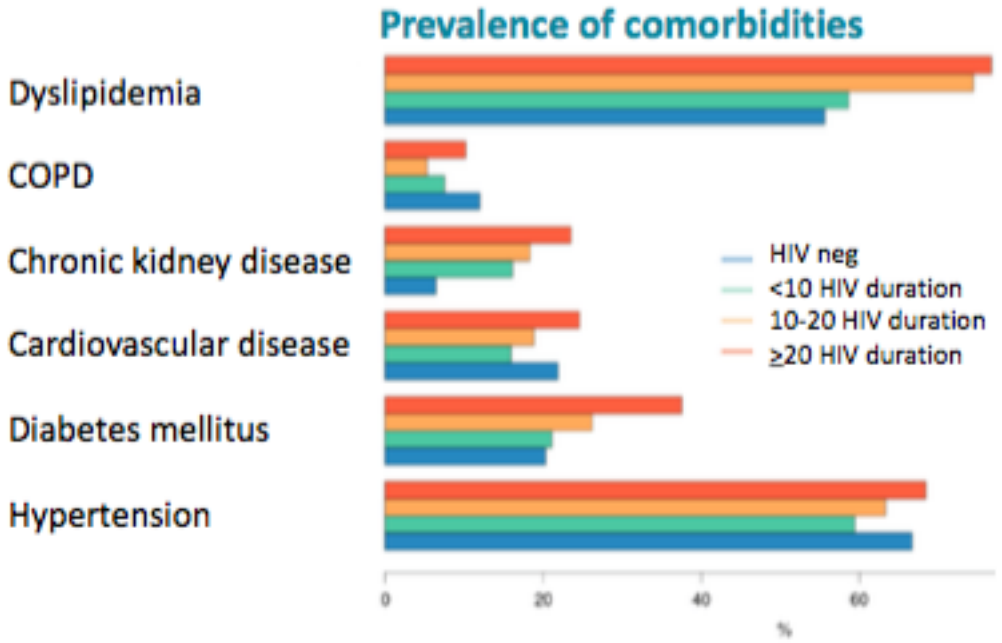
DHHS Guidelines. May 2018.

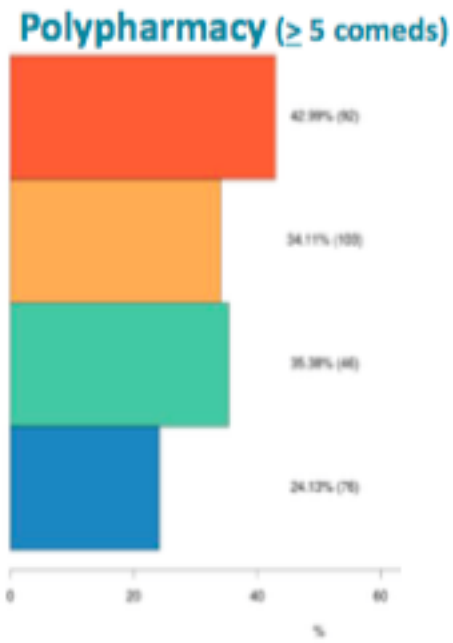
Slide credit: clinicaloptions.com

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)





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 effets
- 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

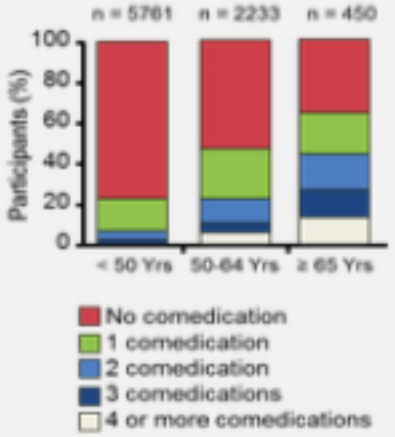
Most common drug classes associated with ADR in elderly:

- Cardiovascular drugs
- Diuretics
- Anticoagulants
- NSAIDs
- Antidiabetics

Geriatric syndromes

- Falls
- Cognitive decline
- Orthostatic hypotension

Drug-drug interactions



older individuals receive more comedications and thus are at higher risk for DDIs

Hasse B et al. CID 2011, Marzolini C et al. JAC 2011, Shah B et al. Clin Geriatr Med 2012, Gellad WF et al. Am J Geriatr Pharmacother 2011

Summary

- Polypharmacy ↑ risk of DDIs, drug related side effects and medications errors
- Elderly particularly at risk due to ↑ age related co-morbidities and age related physiological changes which impact the risk-benefit ratio of many drugs
- For an appropriate management of polypharmacy:
  - **medication reconciliation**
  - **review prescriptions**
    - **indication ==> stop unecessary treatments**
    - **dose (e.g. adapt to renal function)**
    - **duration of treatment**
    - **drug-drug and drug-diseases interactions**
    - **inappropriate drugs**
    - **missing medication**
  - **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


Welcome
Update
UNIVERSITY OF
LIVERPOOL
Liverpool HIV iChart
Providing summary data of HIV drug interactions.
Full details available at
www.hiv-druginteractions.org
Search For Drug Interactions
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Additional Drug–Drug Interactions With ART

	ATV/ RTV	DRV/ RTV	EFV	RPV	DTG	EVG/ COBI	RAL	ABC	FTC	3TC	TDF
Antacids											
PPIs											
Alfuzosin											
Budesonide											
Fluticasone											
Slidenafil											
St John's wort											
Escitalopram											
Aspirin											
Ibuprofen											
Codeine											
Methadone											
Morphine											
Oxycodone											
Tramadol											
Diazepam											
Midazolam											
Pimozide											
Phenytoin											
Rifampicin											

- No clinically significant interaction expected
- These drugs should not be coadministered
- Potential interaction that may require a dosage adjustment
- Potential interaction predicted to be of weak intensity

EACS Guidelines. V7.1. November 2014.

Can we get our patients to age successfully?

D.E. Vance et al.

Clinical Interventions in Aging

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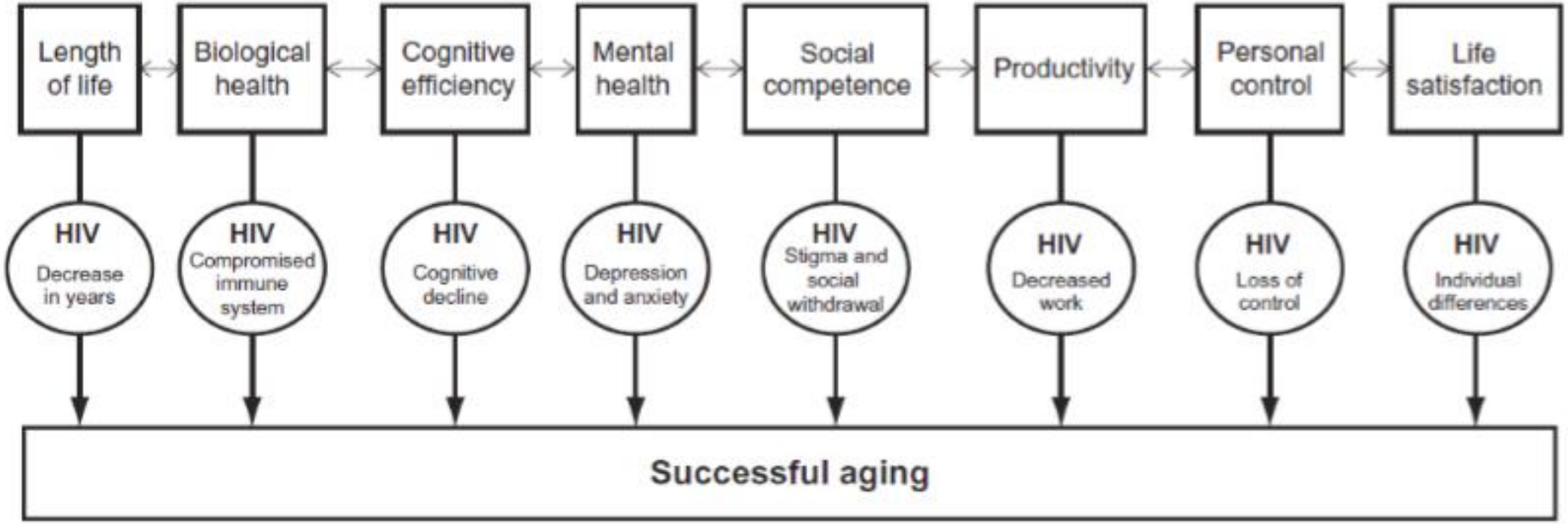
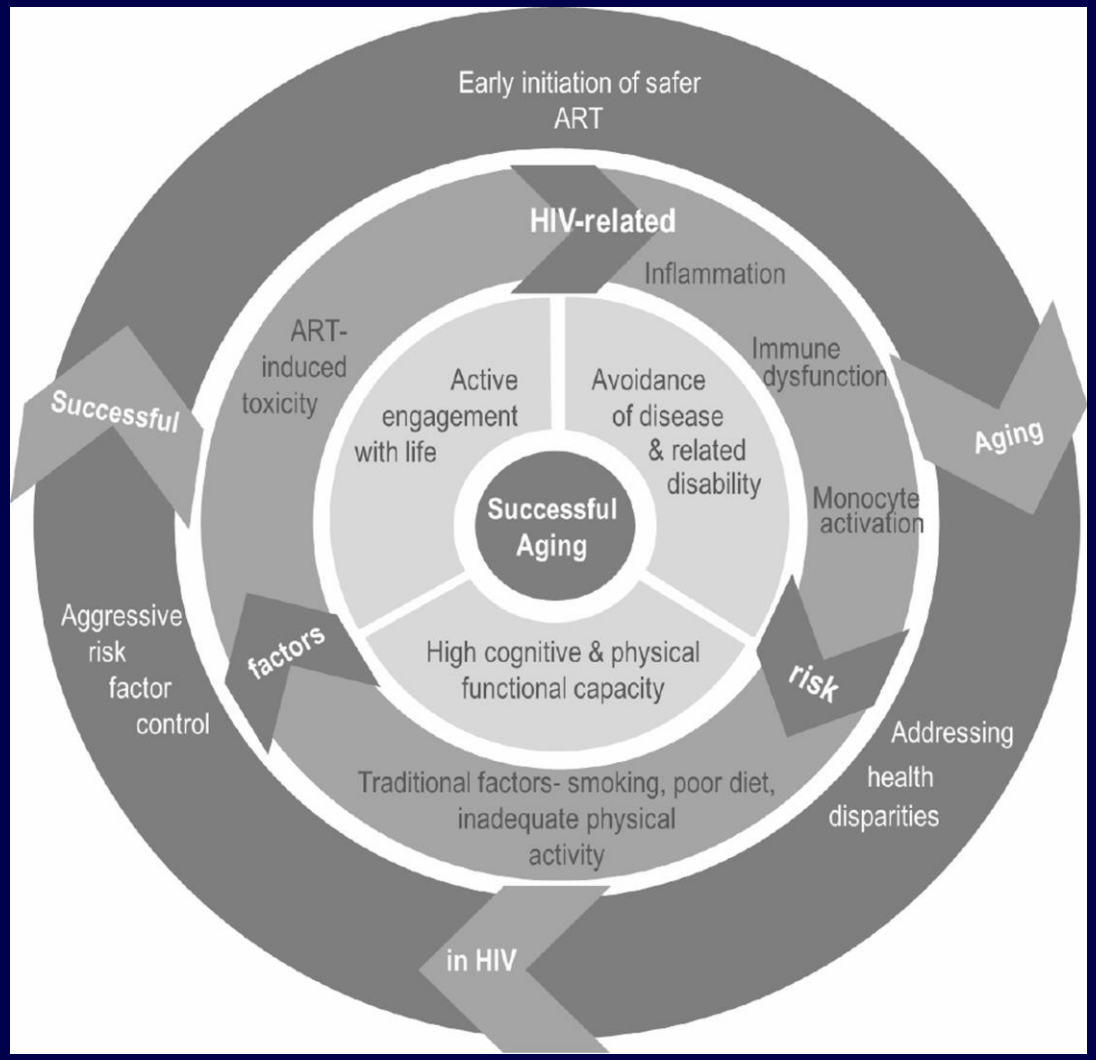
REVIEW

Successful aging and the epidemiology of HIV



ure 1 Factors of and obstacles to successful aging with HIV.

Figure 1



International Journal of Infectious Diseases 2018 66, 56-64DOI: (10.1016/j.ijid.2017.11.010)

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

DHHS Guidelines. May 2018.

Slide credit: clinicaloptions.com

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]

1. Hermsdorff HH, et al. Endocrine. 2009;36:445-451. 2. Bonato M, et al. BMC Infect Dis. 2017;17:61.
3. Sigel K, et al. Curr HIV/AIDS Rep. 2011;8:142-152. 4. NCI. HIV infection and cancer risk. 5. USPSTF. Breast cancer: screening. January 2016. 6. Mani D, et al. Curr Opin Oncol. 2013;25:518-525.

OPINION

Achieving the fourth 90: healthy aging for people living with HIV

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