

Managing Comorbidities in People with HIV

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Disclosures

- The speaker has no conflicts of interest to disclose.

Objectives

- Describe the current comorbidity profile for persons with HIV and implications for long-term care.
- Discuss assessment and intervention for HIV related cardiovascular disease, cancers, cognitive decline, metabolic, renal, hepatic, and bone health conditions.
- Discuss the integration of comorbidity management into routine HIV care through interprofessional practice.
- Examine the need for consultation and co-management with cardiology, oncology, neurology, and geriatrics.

The Changing Face of HIV

The Changing Face of HIV

- Effective antiretroviral therapy (ART) has transformed HIV infection into a chronic illness
- Survival of people with HIV who receive treatment is now similar to the general population
- These treatment successes have resulted in a large number of older adults with HIV.
 - Approximately 50% of people living in the United States are over age 50.

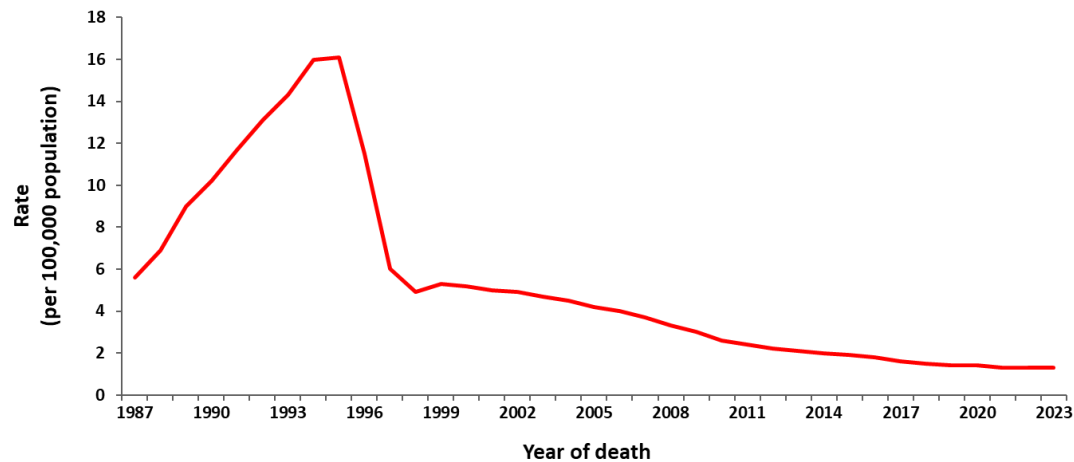
AGING AND HIV

Thanks to effective **HIV treatment**, the number of **older adults** living with HIV is **increasing**.

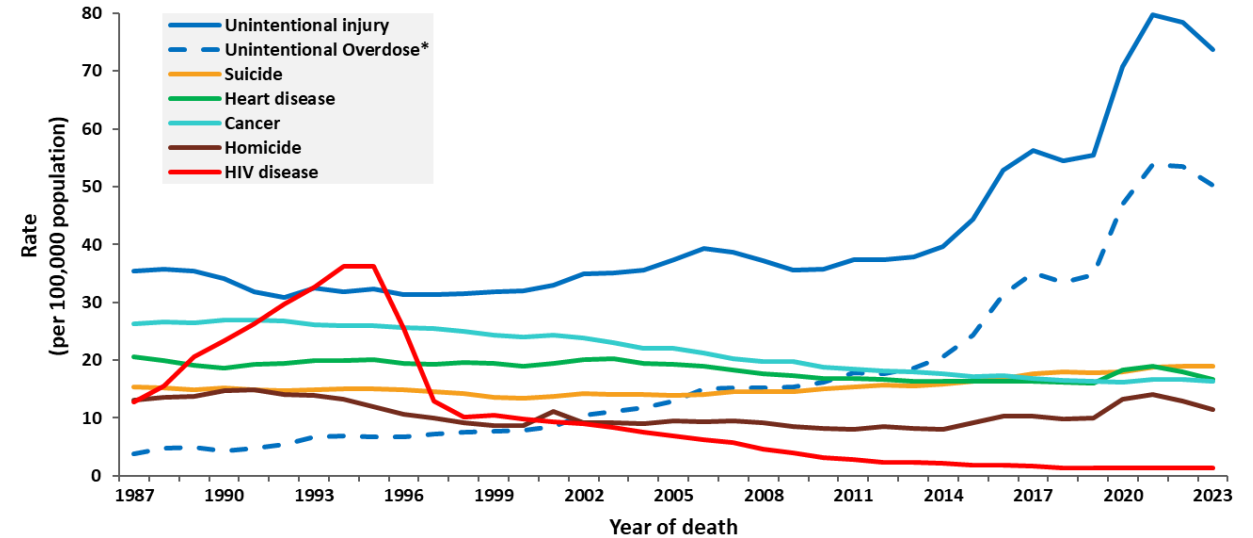


Changes in HIV Mortality

Age-adjusted rates of death in the general population with HIV disease as the underlying cause, 1987–2023—United States

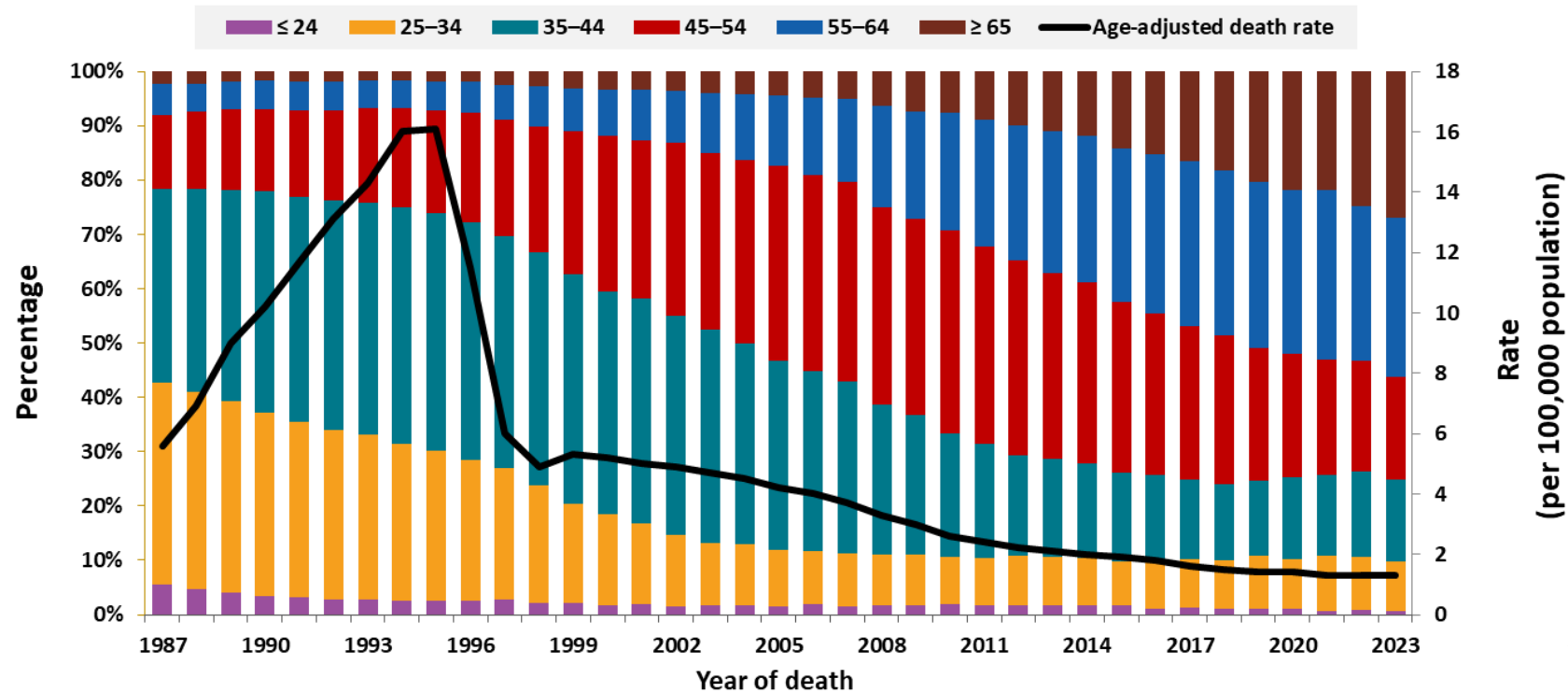


Deaths in the general population with HIV disease as the underlying cause versus the leading causes among persons aged 25–44 years, 1987–2023—United States



Changes in HIV Mortality

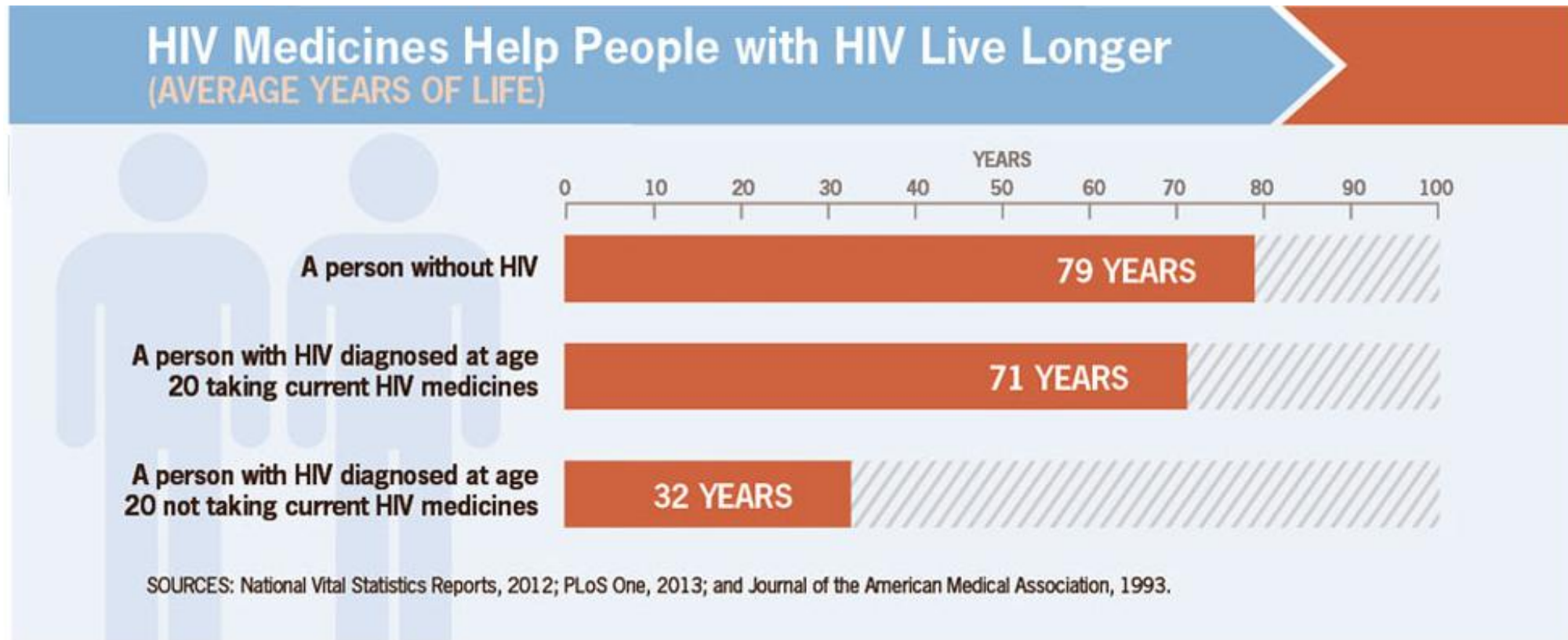
Age-adjusted rates and percentage distribution of deaths in the general population with HIV disease as the underlying cause by age group, 1987–2023—United States



Note. Data from CDC WONDER Online Database based on death certificate data compiled by the National Center for Health Statistics.

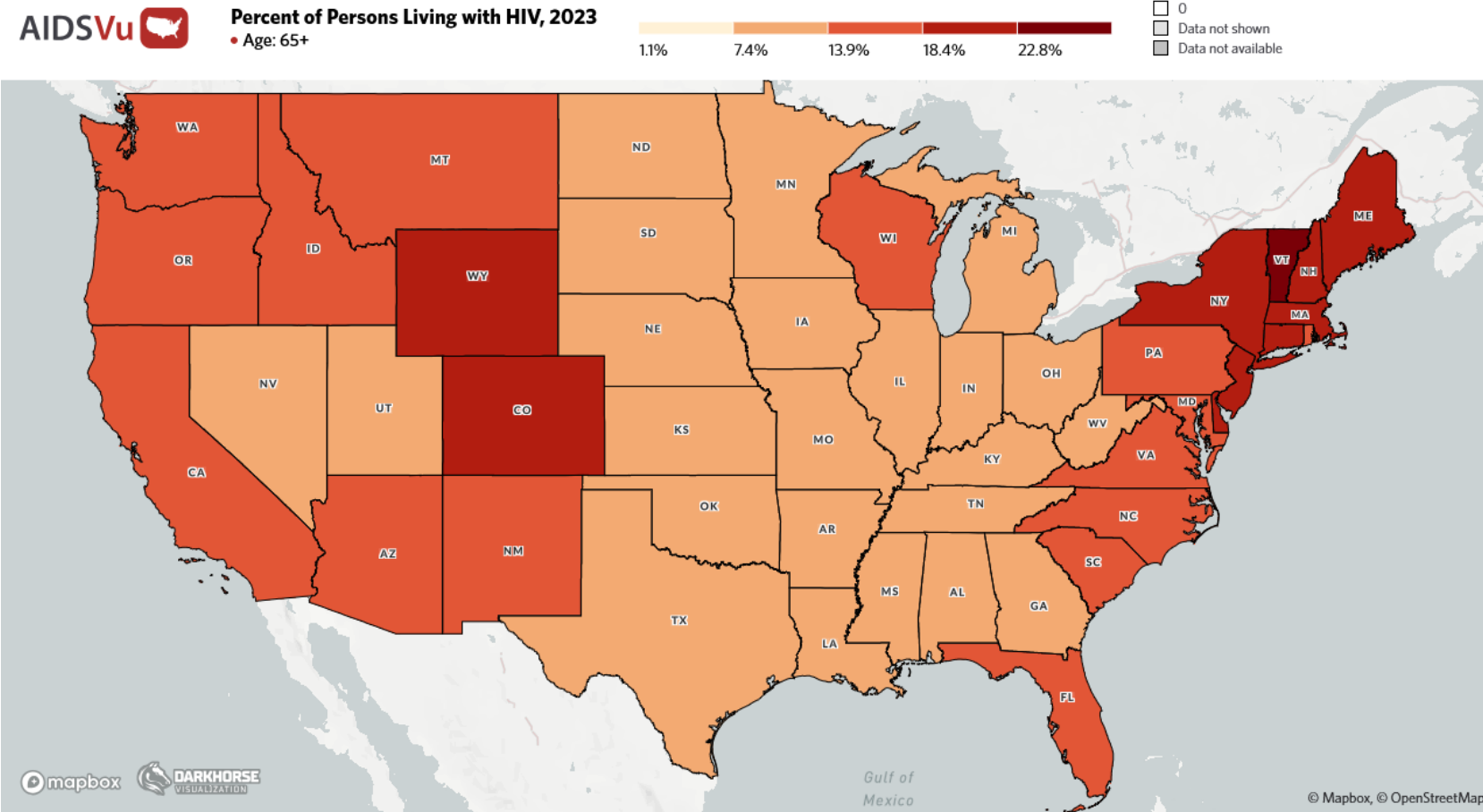


Changes in HIV Mortality



<http://www.cdc.gov/vitalsigns/hiv-aids-medical-care>

Aging HIV Population in the United States



https://map.aidsvu.org/prev/state/prop/age_65over/none/usa?geoContext=national

The Changing Face of HIV

1980's



1990's



Today



Non-Infectious Comorbidities

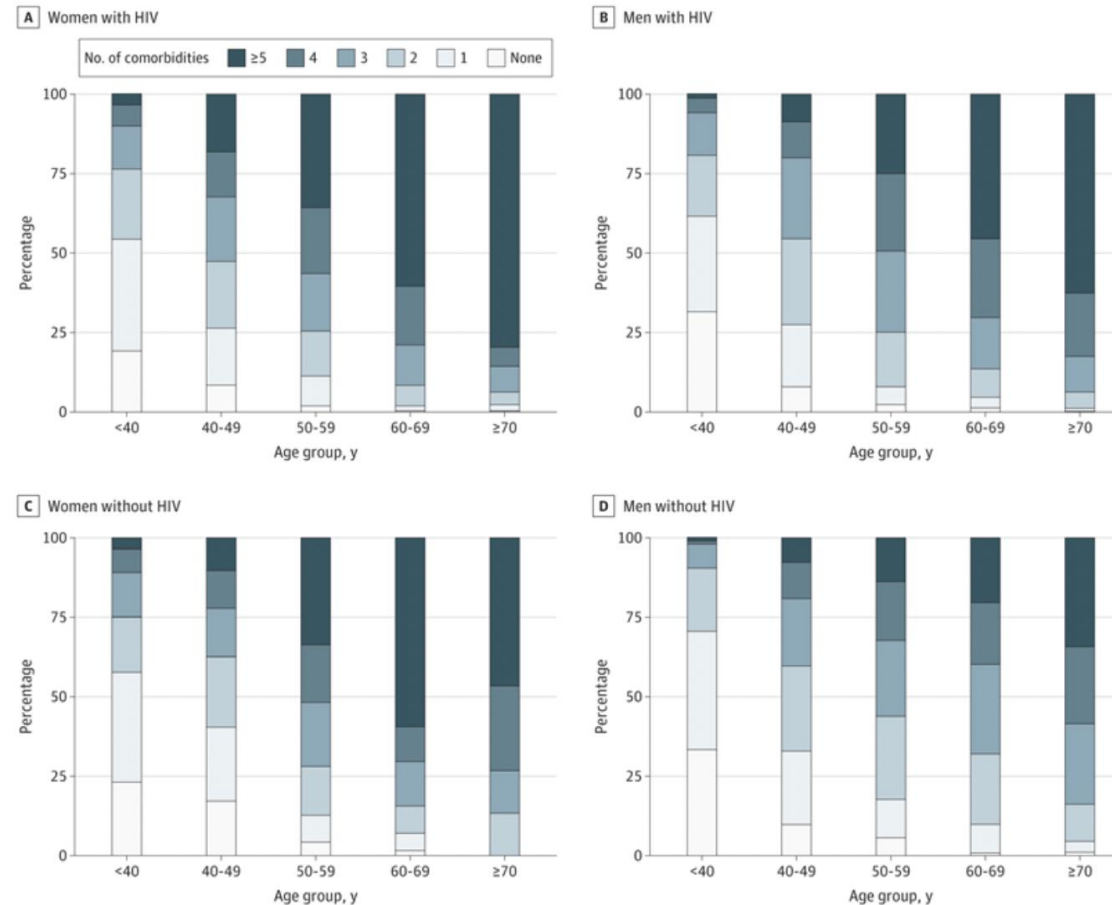
- Have overtaken opportunistic infections as major cause of morbidity and mortality in patients with HIV
- HIV infection is associated with high rates of comorbid conditions and functional decline
- Increased risk of developing co-morbid conditions occurs despite good virologic suppression
- People with HIV develop some age-associated conditions at younger ages than their uninfected counterparts

Non-Infectious Comorbidities

- Comorbid conditions affect multiple organ systems
- Include
 - Liver disease
 - Cardiovascular disease
 - Renal disease
 - Non-HIV associated malignancies
 - Osteoporosis
 - Neurocognitive decline
 - “Frailty”

Non-Infectious Comorbidities

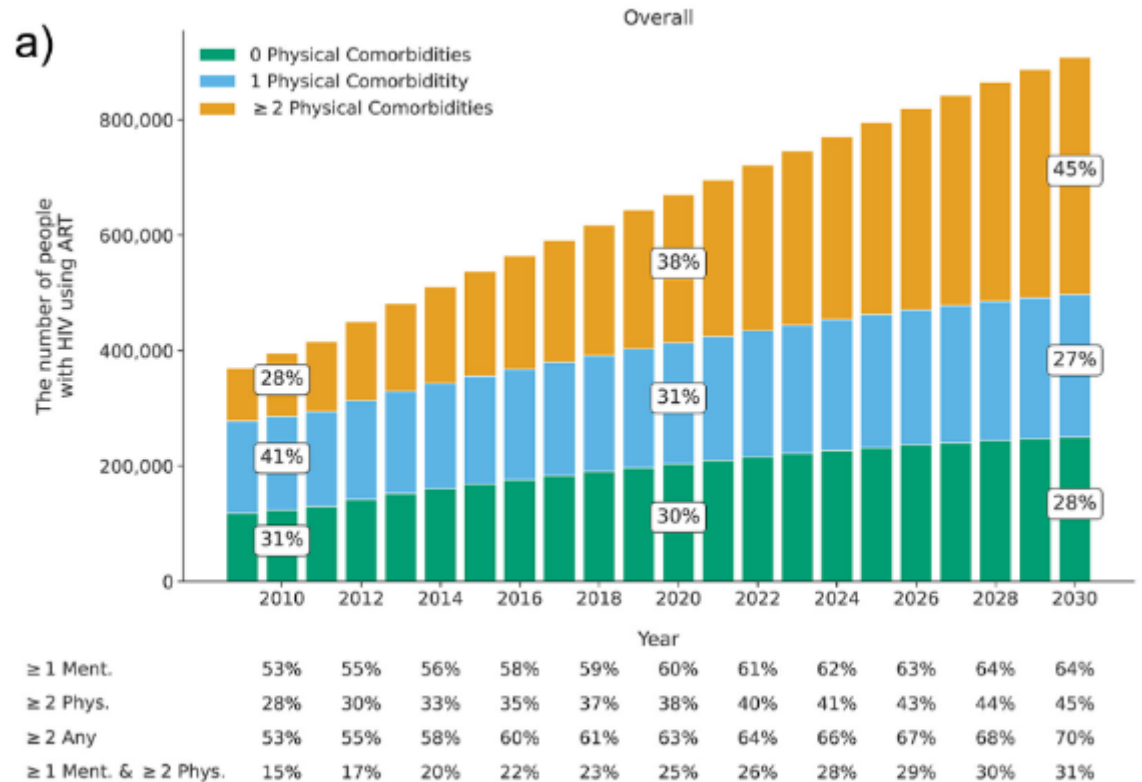
Figure 1. Distribution of Prevalent Non-AIDS Comorbidity (NACM) Burden by HIV Serostatus, Sex, and Age Group



Collins LF et al. JAMA Network Open. 2023;6(8):e2327584.

Increasing Prevalence of Comorbidities

- Modeling study forecasting an increased prevalence of multimorbidity among people with HIV who are on treatment.
 - Includes 9 prevalent diagnoses that require clinical management.
- Mental health diagnoses, particularly depression and anxiety play a major role.
- Influenced by age distribution, and physical and behavior risk factors.



Althoff et al. 2024. PLOS Medicine

Comorbid Conditions in People with HIV on Medicare

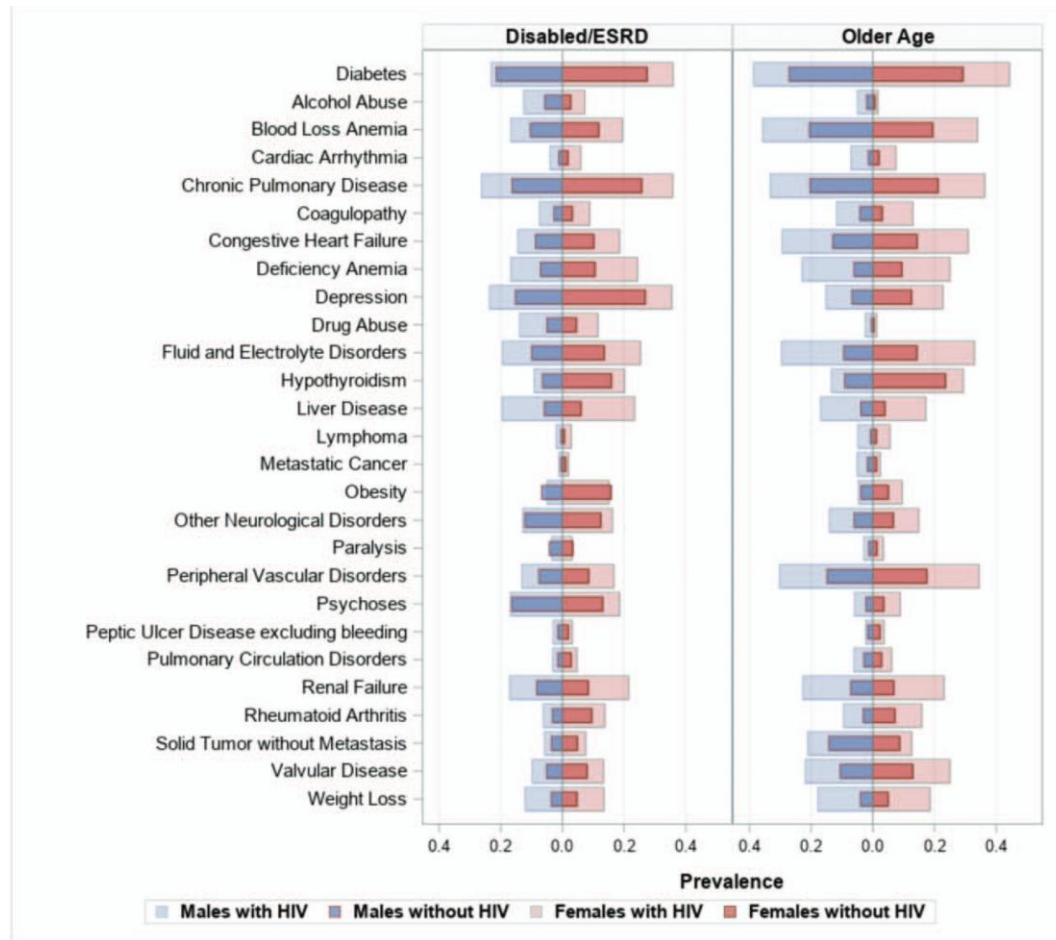
- Retrospective national matched cohort study of Medicare beneficiaries between 1996 and 2015
- Compared baseline comorbidities and mortality between HIV-infected and uninfected individuals stratified by sex and original entitlement

Assessing comorbidities and survival in HIV-infected and uninfected matched Medicare enrollees

Xiaoying Yu^{a,b}, Jordan R. Westra^a, Thomas P. Giordano^{c,d},
Abbey B. Berenson^{b,e}, Jacques G. Baillargeon^a
and Yong-Fang Kuo^{a,b}

Yu et al. 2021. AIDS

Comorbid Conditions in People with HIV on Medicare

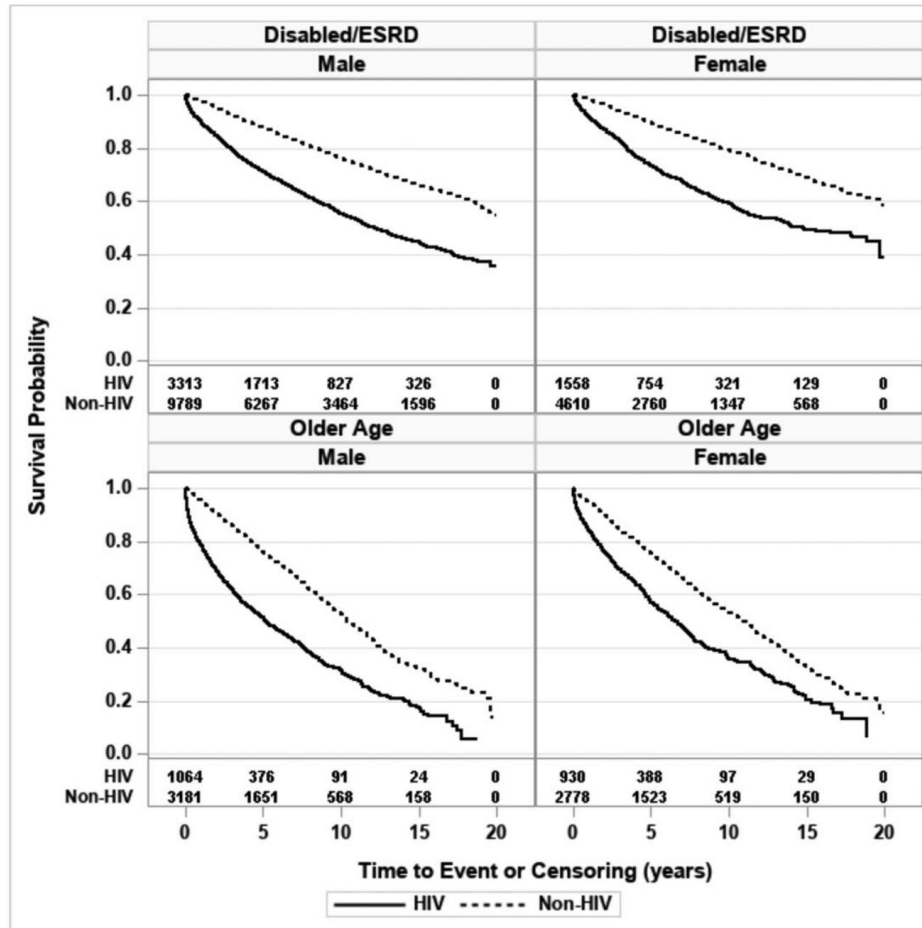


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Yu et al. 2021. AIDS

Comorbid Conditions in People with HIV on Medicare

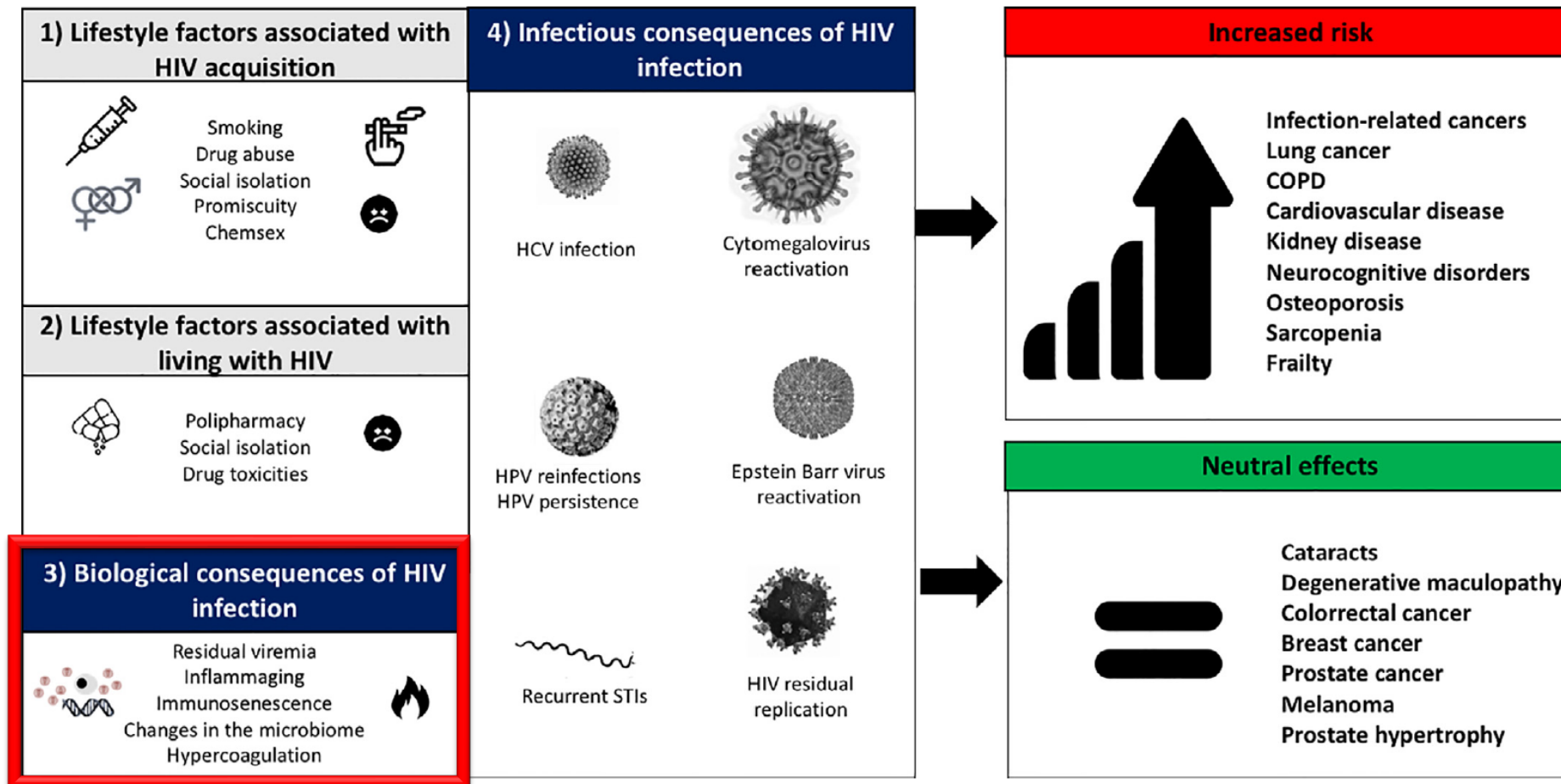


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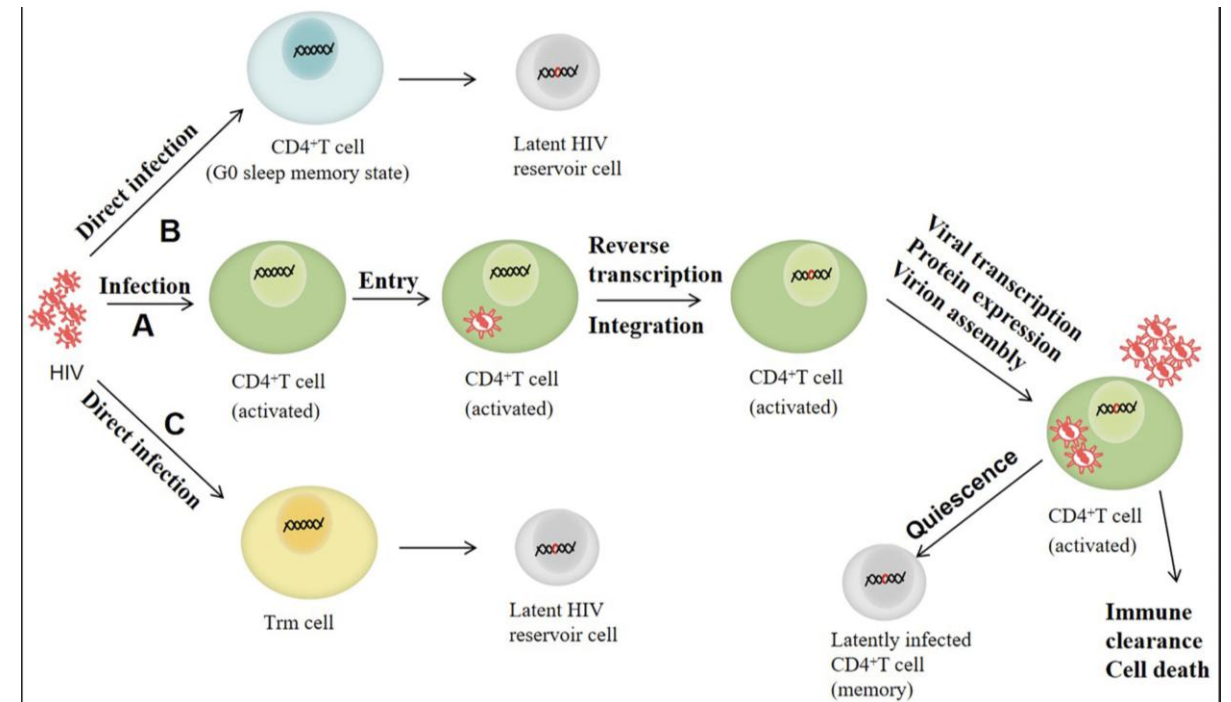
Yu et al. 2021. AIDS

Risk Factors and Comorbid Conditions



Persistent Immune Activation

- Modern ART enables rapid control of HIV replication and improved immune function
 - Does NOT fully restore immune health
- During primary infection, HIV infects a large number of CD4+ cells, including activated memory cells
 - Establishes an HIV-1 Latent Reservoir
 - Causes significant depletion of CD4+ T cells from mucosal associated lymphoid tissues (MALT)



Chen et al. 2022. *Frontiers in Cellular and Infection Microbiology*

Persistent Immune Activation

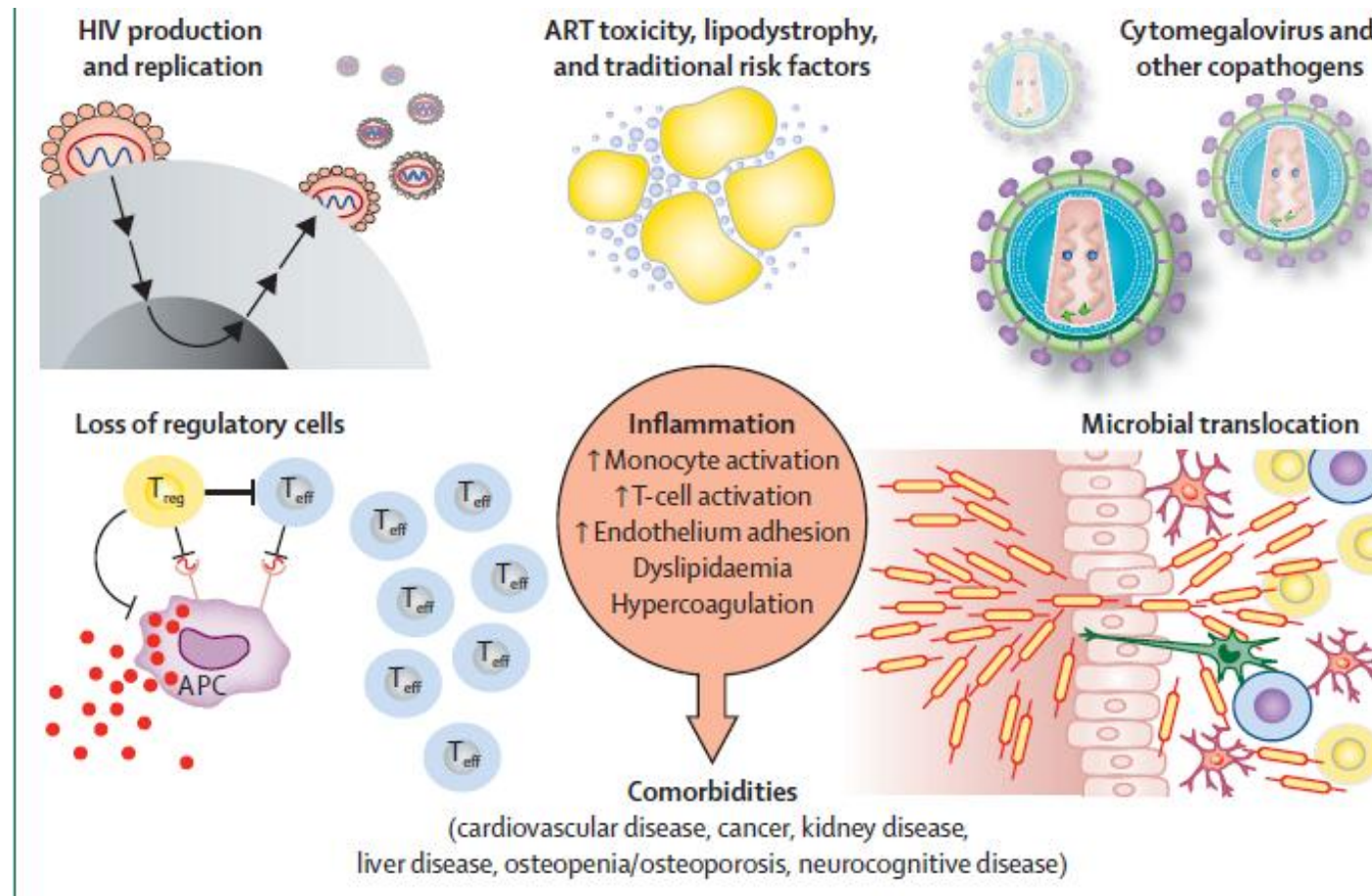
Sources for ongoing immune activation in patients with HIV infection

- Recurrent stimulation of immune cells that recognize HIV components
- Reactivation of other common latent viruses
 - CMV, EBV, HSV, HPV
- Disrupted mucosal lymphoid tissues allowing microbial translocation from the GI tract

Chronic activation of inflammatory markers in patients with HIV

- IL-6, soluble CD-14
- Associated with increased mortality

Persistent Immune Activation



HIV and “Accelerated Aging”

- Biological mechanisms of aging have been demonstrated to occur at higher rates in people with HIV compared to uninfected individuals
 - Mitochondrial dysfunction
 - Telomere shortening
 - Epigenetic changes
- Uncertainty remains if these changes cause premature or “accelerated” aging and how/if they are impacted by ART.

HIV and “Accelerated Aging”

- Examined epigenetic aging over the course of initial HIV infection with samples from participants in the **Multicenter AIDS Cohort Study**
- 5 epigenetic measures of aging before and after HIV infection in comparison with matched uninfected controls
- Found that multiple epigenetic measures in peripheral blood mononuclear cells were significantly different after initial HIV infection

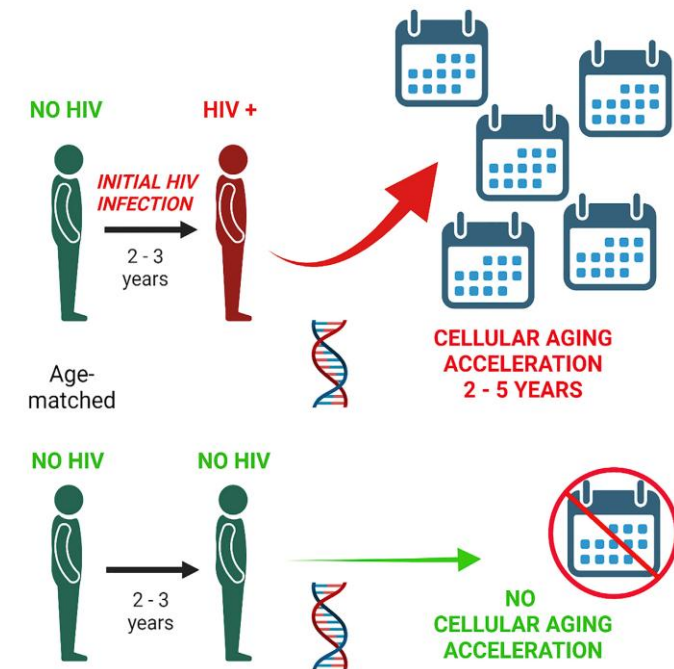
iScience

CellPress
OPEN ACCESS

Article

Accelerated aging with HIV begins at the time of initial HIV infection

Elizabeth Crabb Breen,¹ Mary E. Sehl,² Roger Shih,² Peter Langfelder,^{3,4} Ruibin Wang,^{5,13} Steve Horvath,^{6,7} Jay H. Bream,⁸ Priya Duggal,⁵ Jeremy Martinson,⁹ Steven M. Wolinsky,¹⁰ Otoniel Martínez-Maza,¹¹ Christina M. Ramirez,¹² and Beth D. Jamieson^{2,14,*}



Clinical Manifestations



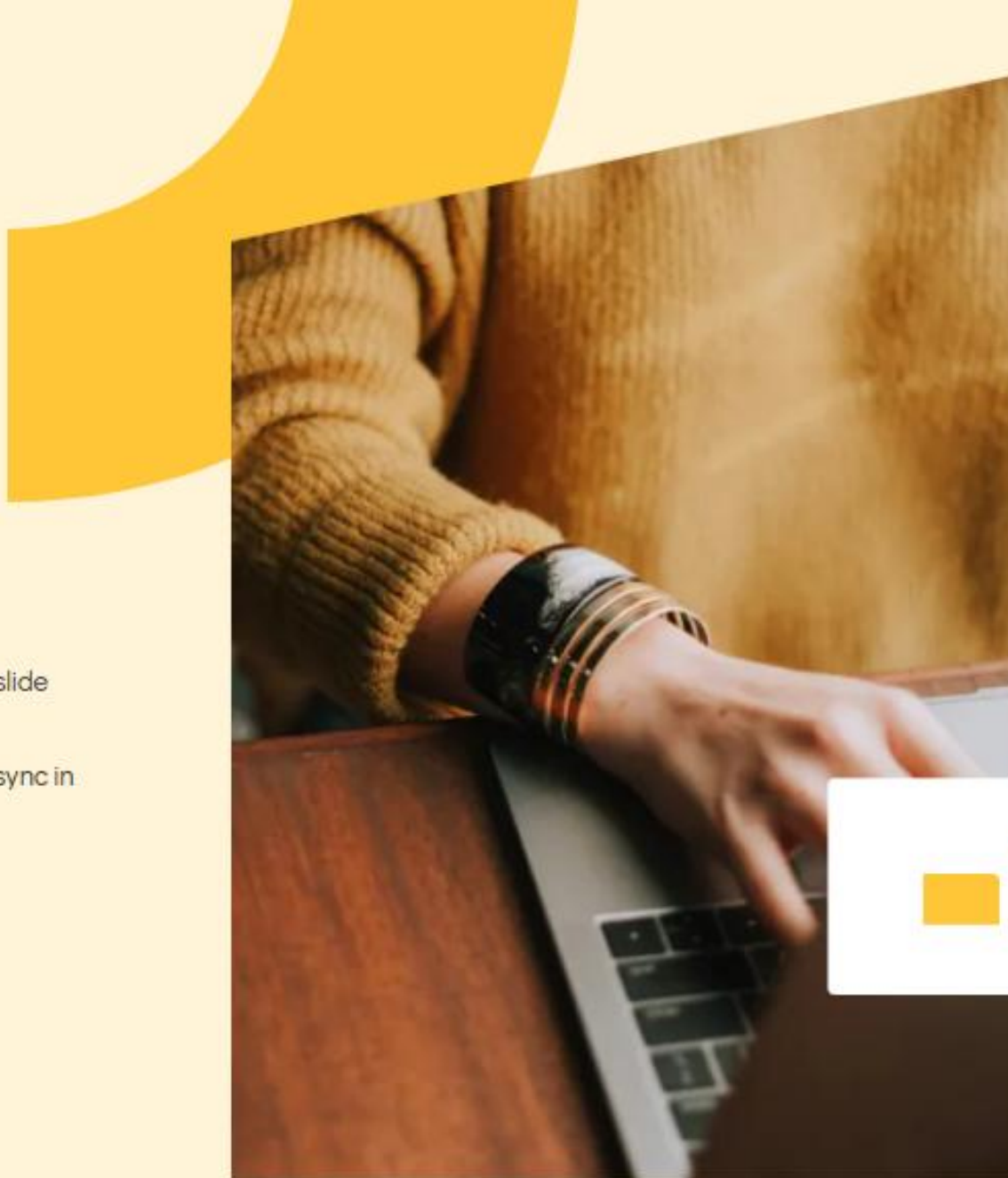
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Case 1.

- A 52-year-old male presents to the emergency department with substernal chest discomfort for the past 4 hours
 - He has a past medical history significant for hypertension and HIV infection
 - HIV initially diagnosed in 1999. Currently on antiretroviral therapy with undetectable viral load and CD4 count of 548.

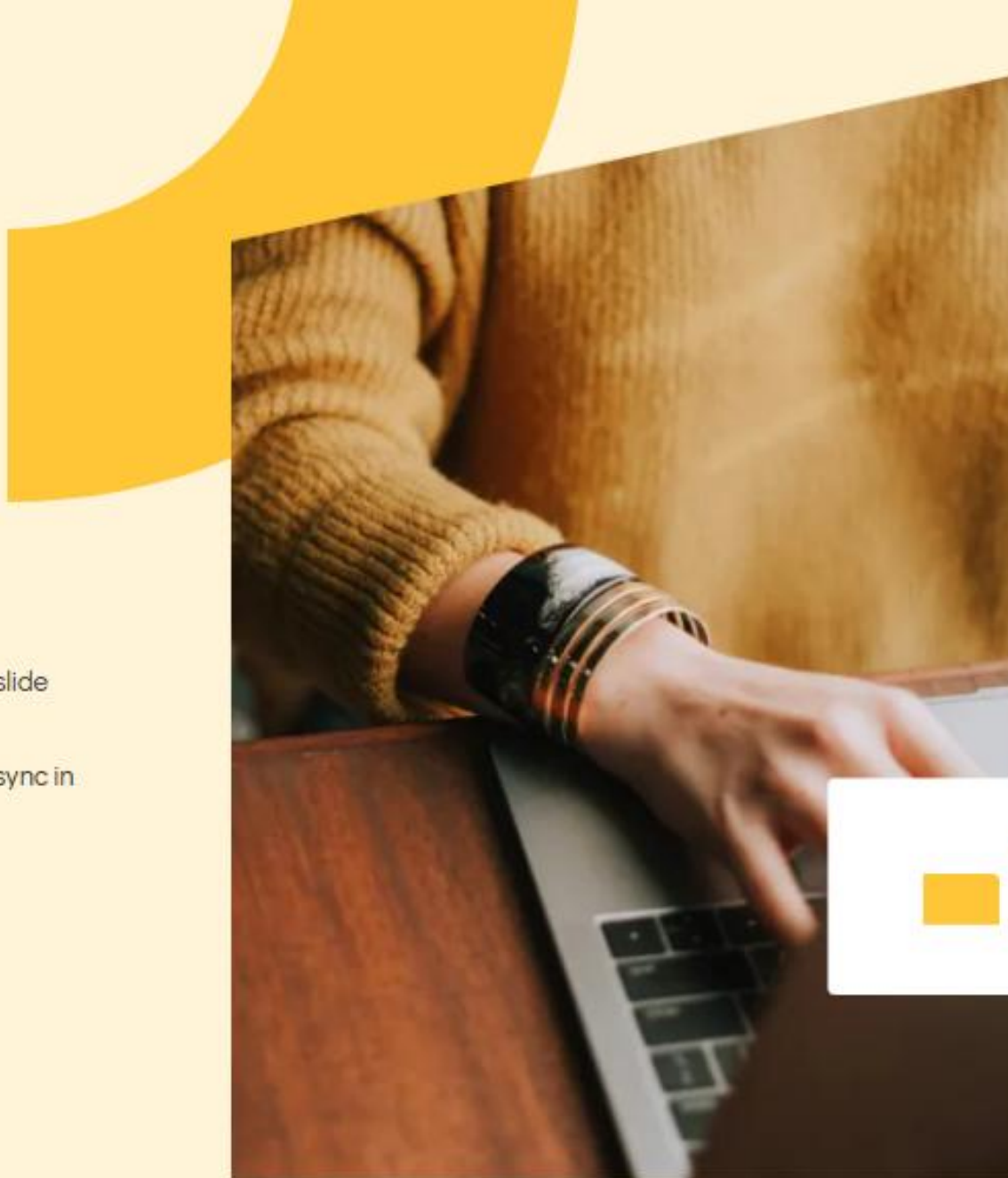
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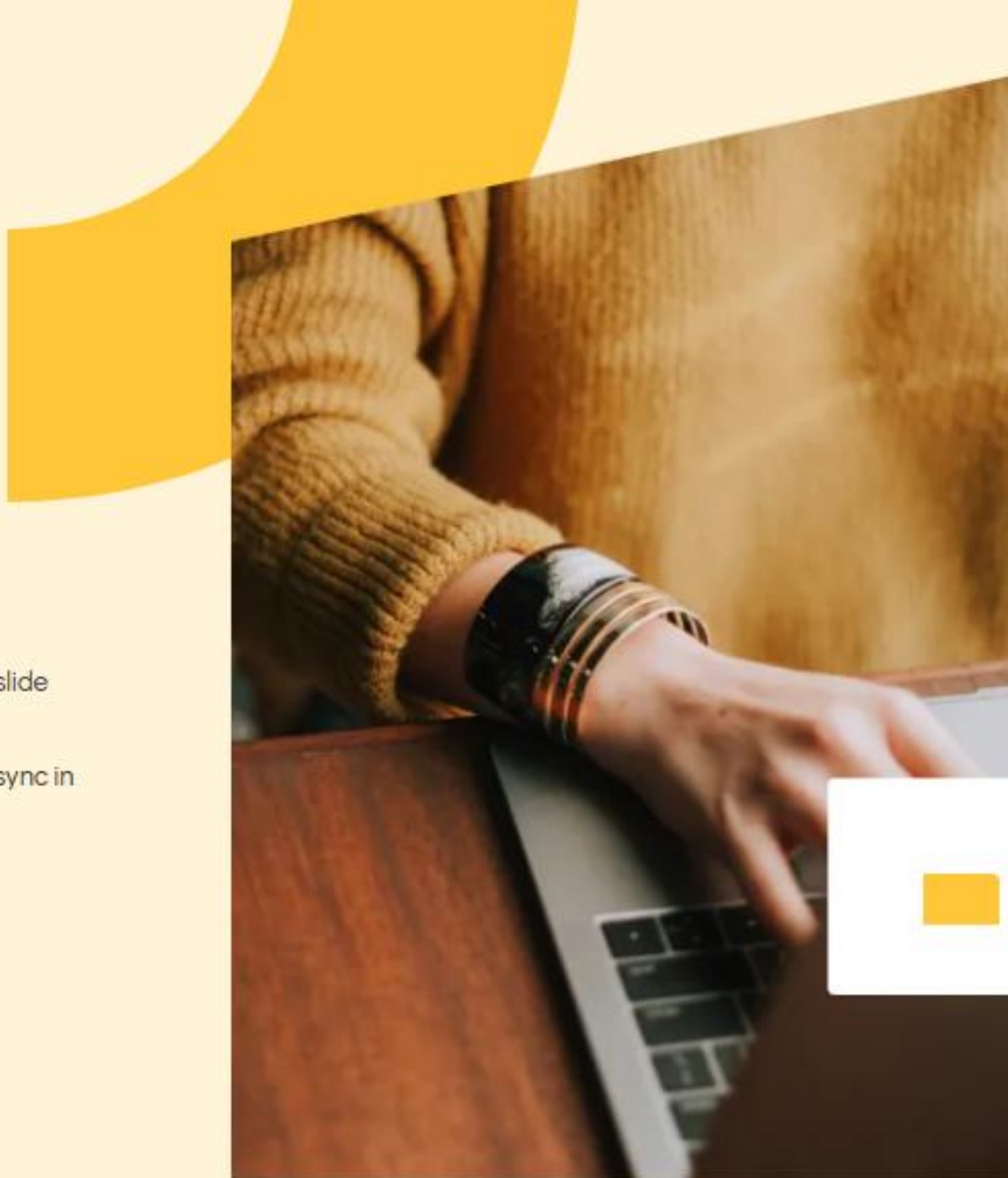
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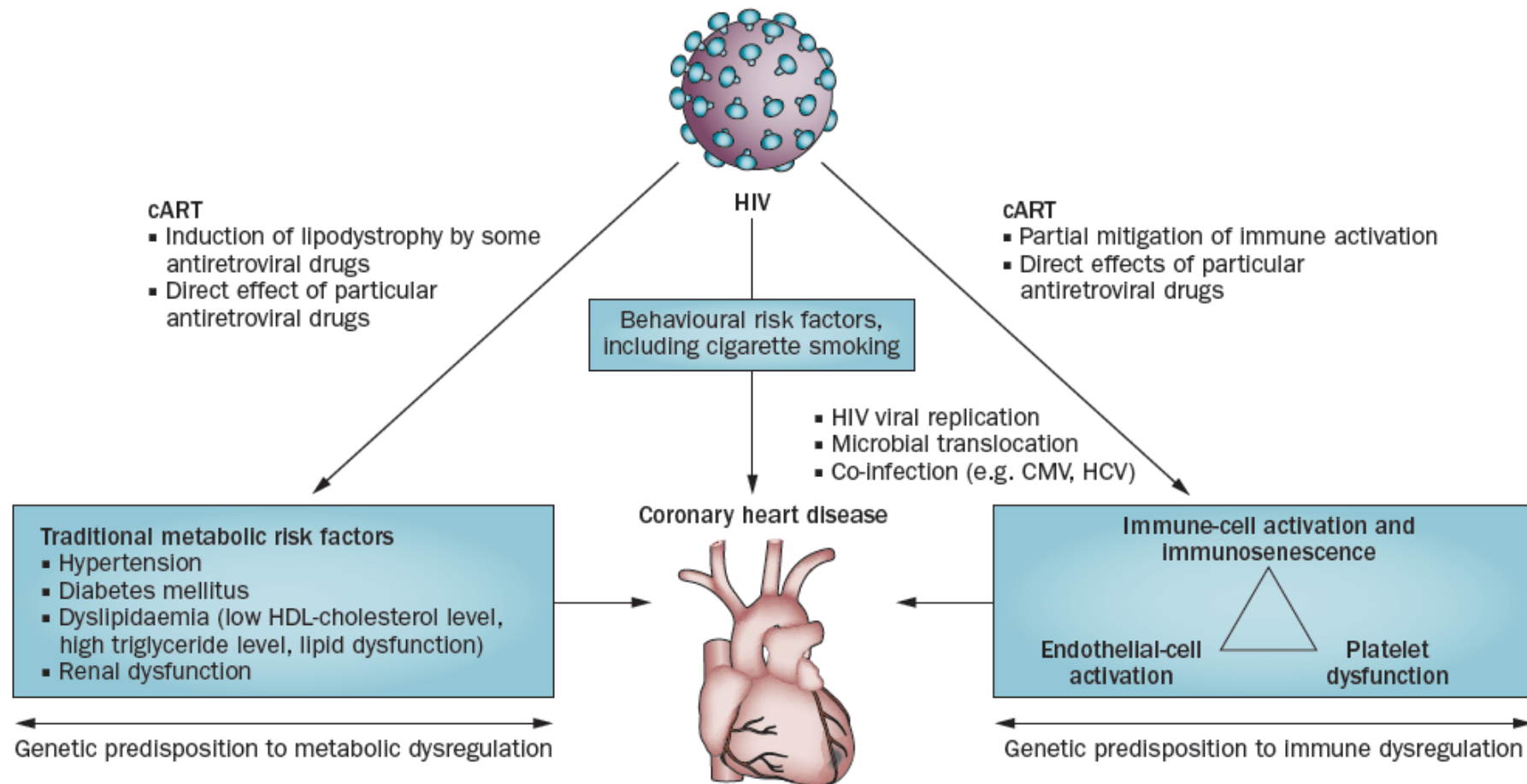
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HIV and Cardiovascular Disease

- In high income countries, coronary heart disease is one of the leading cause of death in patients with HIV infection who are on ART
- HIV infection is associated with 50% increase in the risk of acute MI beyond that explained by other recognized risk factors
 - Including patients who are taking ART
- Pathophysiology is multifactorial

Feinstein et al. American Journal of Cardiology. 2016
Freiberg et al. JAMA Internal Medicine 2013
Drozdz et al. JAIDS 2017
Shah, Circulation. 2018

HIV and Cardiovascular Disease



HIV and Cardiovascular Disease

Traditional cardiovascular risk factors

- Hypertension
- Diabetes mellitus – Mixed data
- Dyslipidemia
- Renal dysfunction

Smoking

- Rates of tobacco use are higher in people with HIV
- Contribution of smoking to the risk of acute coronary syndrome is 2x higher

*Kaplan et al. Clinical Infectious Disease. 2007, Dube & Fenton. Clinical Infectious Diseases. 2003
Pujari et al. JAIDS 2005, Triant et al. Journal of Clinical Endocrinology and Metabolism. 2007
Seaberg et al. AIDS. 2005, Frazier et al. Annals of Internal Medicine. 2015
Brown et al. 2005. Archives of Internal Medicine, Mdodo et al. Annals of Internal Medicine. 2015
Jotwani et al. American Journal of Kidney Disease. 2011. Calvo-Sanchez et al. HIV Medicine. 2013*

REPRIEVE Trial

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

AUGUST 24, 2023

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Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D.,
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 Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H.,
 Heather J. Ribaud, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

REPRIEVE TRIAL

Phase 3 multinational, randomized, placebo-controlled trial to assess the prevention of cardiovascular events in people with HIV and **low-to-moderate** risk of cardiovascular disease.

Included 7769 participants with HIV infection who were stable on antiretroviral therapy.

- Age 40-75 years
- Median LDL of 108 mg/dl
- Median follow-up 5 years

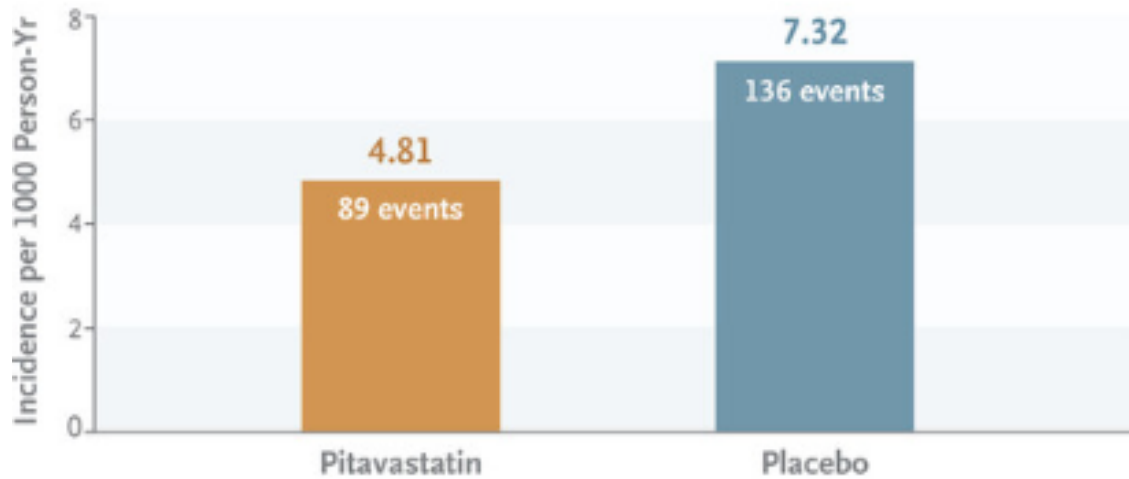
Primary outcome: Occurrence of major adverse cardiovascular event

- Death, MI, Stroke, Peripheral arterial ischemia, Revascularization, Death from undetermined cause

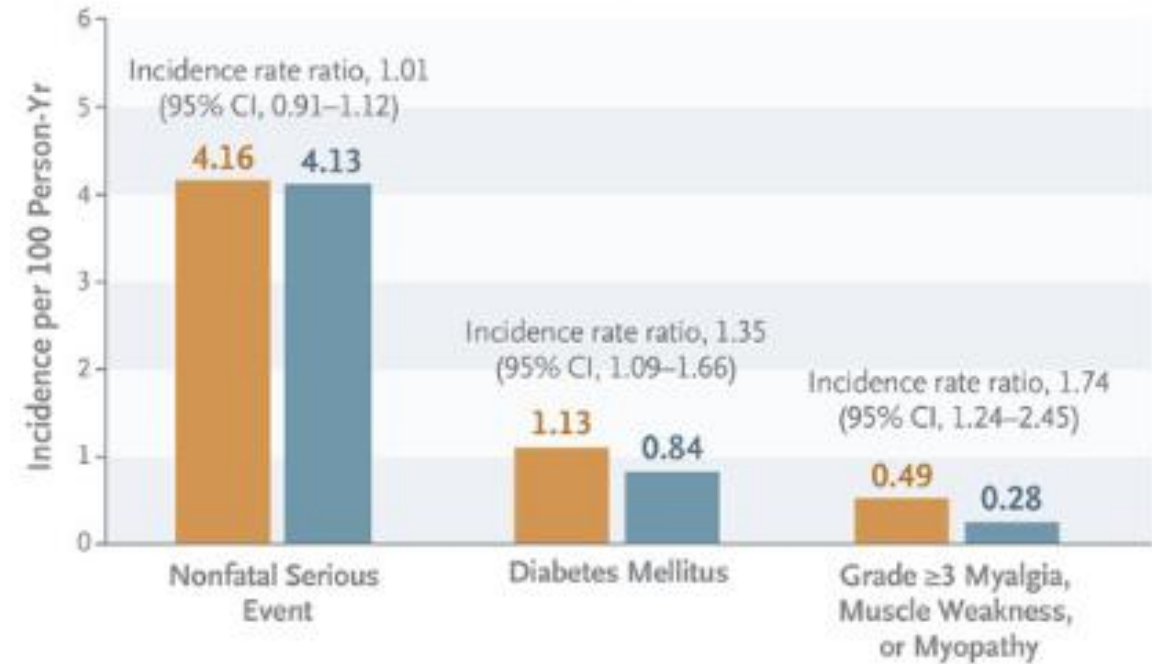
REPRIEVE Trial

Major Adverse Cardiovascular Events

HR, 0.65 (95% CI, 0.48–0.90); P=0.002



Adverse Events



REPRIEVE Trial

- Participants in the statin group had a lower incidence of major adverse cardiovascular events than those in the placebo group
 - Hazard reduction of 35% over 5 years
 - Reduction was larger than predicted based on observed reductions in LDL cholesterol levels
- **Trial discontinued early due to observed benefit of statin therapy.**

Clinical Guideline Update

Recommendations for the Use of Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People With HIV

For People With HIV Who Have Low-to-Intermediate (<20%) 10-Year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimates 

- Age 40–75 Years
 - When 10-year ASCVD risk estimates are 5% to <20%, the Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (the Panel) recommends initiating at least moderate-intensity statin therapy **(AI)**.
 - Recommended options for moderate-intensity statin therapy include the following:
 - Pitavastatin 4 mg once daily **(AI)**
 - Atorvastatin 20 mg once daily **(AII)**
 - Rosuvastatin 10 mg once daily **(AII)**
 - When 10-year ASCVD risk estimates are <5%, the Panel favors initiating at least moderate-intensity statin therapy **(CI)**. The absolute benefit from statin therapy is modest in this population; therefore, the decision to initiate a statin should take into account the presence or absence of HIV-related factors that can increase ASCVD risk.^a

Case 2.

- 53-year-old female patient presents for evaluation of change in bowel habits, abdominal pain, rectal pain, and rectal bleeding
 - Intermittently occurring for past one year
 - 2-3 bowel movements per day with small amounts. Accompanied by straining and cramping
 - CT scan of the abdomen 2 months ago was reportedly normal
- History of HIV infection diagnosed in 1992.
 - On ART since that time with undetectable viral loads

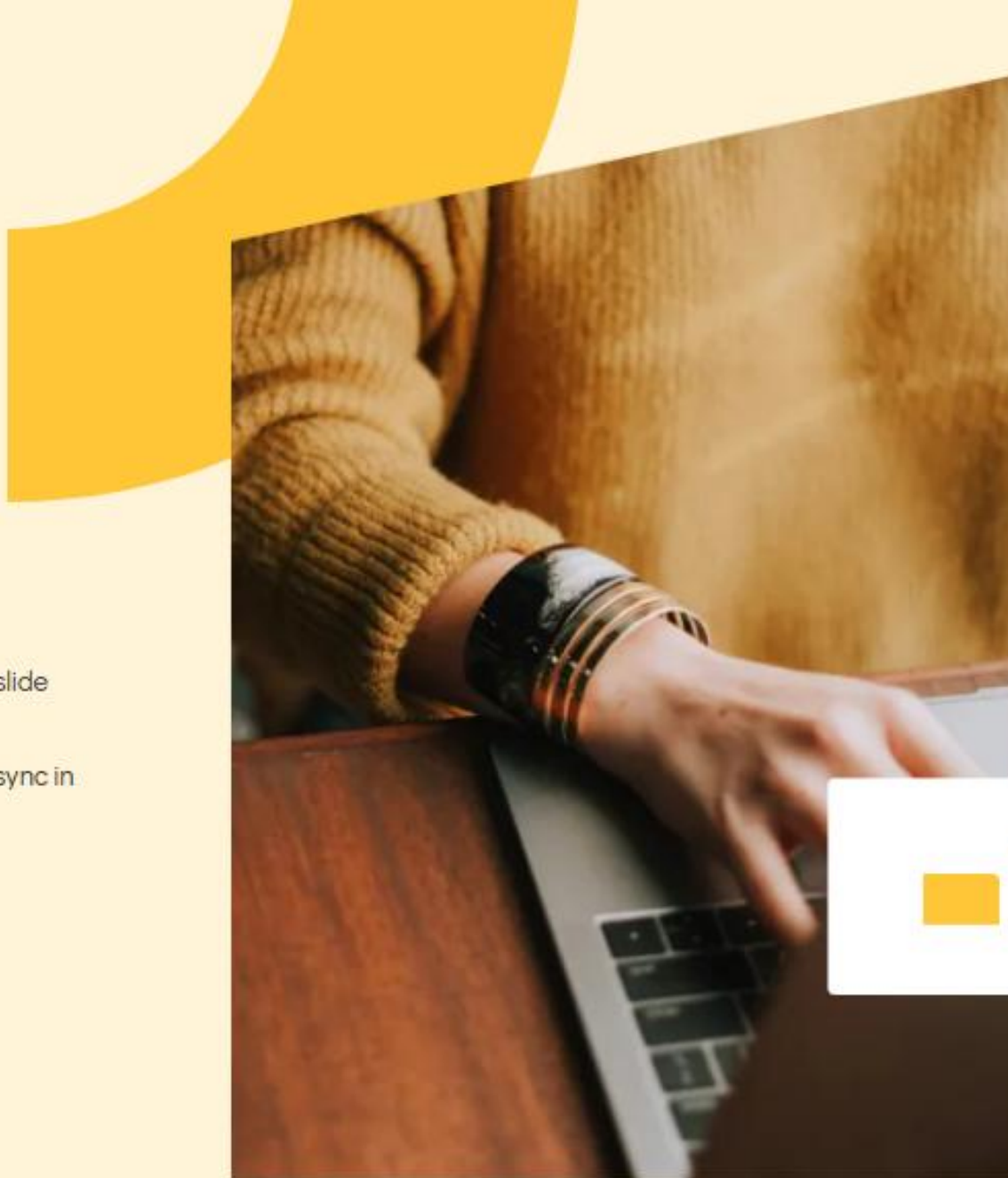
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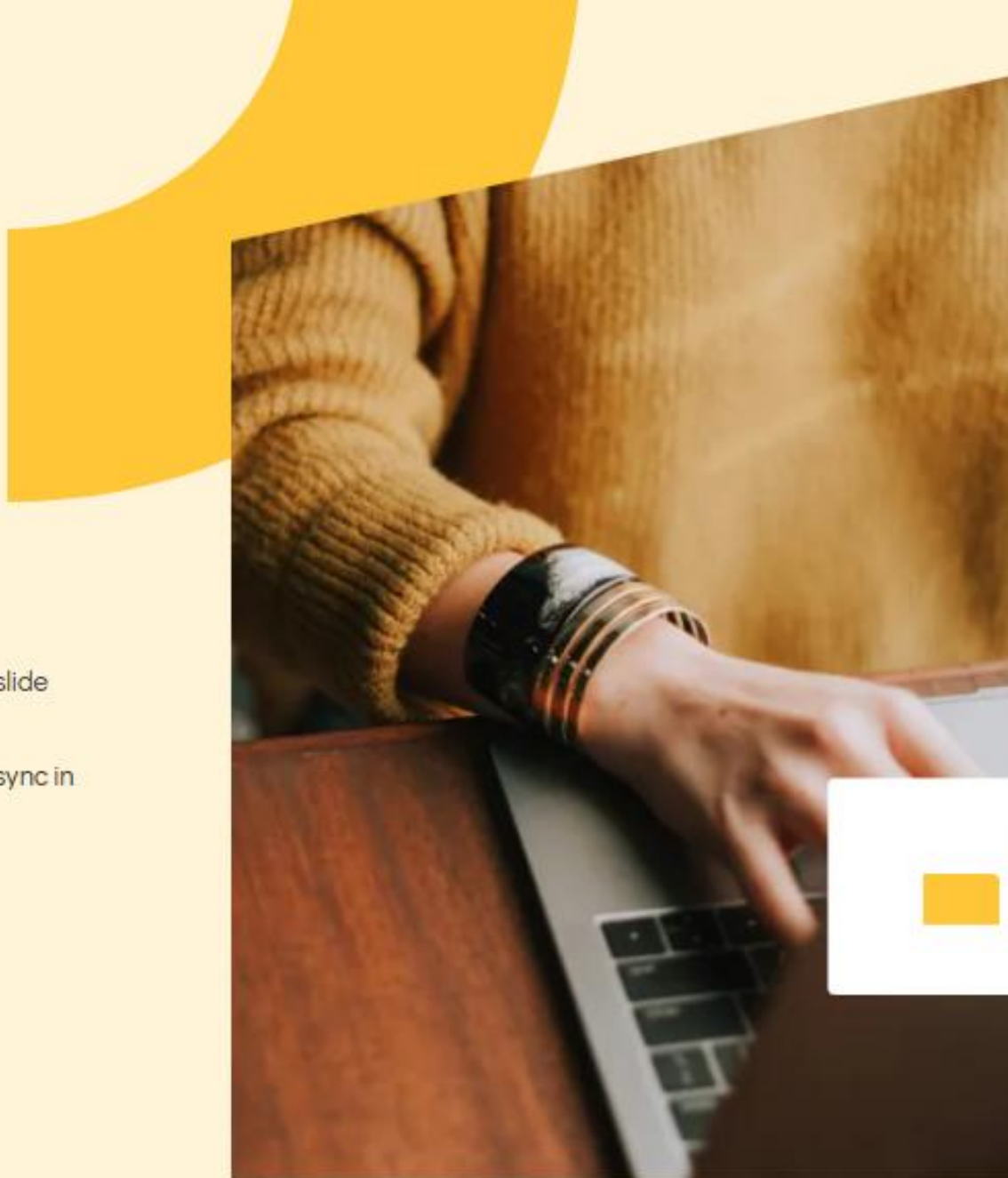
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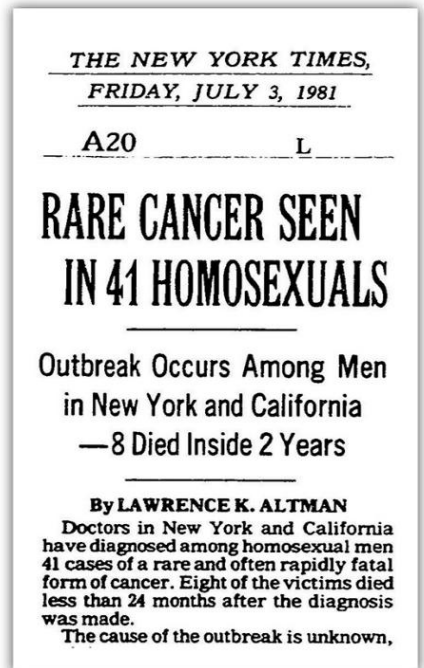
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HIV and Malignancy

- HIV and cancer have been inextricably linked since its discovery
- AIDS Defining Malignancies (ADM):
 - Kaposi's Sarcoma
 - Non-Hodgkin's Lymphoma
 - Cervical Cancer
- Advent of ART led to rapid decline in incident of AIDS defining malignancies
- Decrease in ADM accompanied by concomitant rise in incidence of other malignancies
 - Currently account for 1/3 of the deaths in people with HIV



HIV and Malignancy

Increased Prevalence of Traditional Risk Factors

- Tobacco and Alcohol Use
- Co-infection with Oncogenic Viruses
 - Shared transmission routes
 - More susceptible to oncogenic effects of viruses

Factors Specific to HIV Infection

- Direct HIV Effects
- Immunosuppression
 - Decreased tumor surveillance
 - Strongest link for KS and NHL
- Inflammation

HIV and Malignancy

- Many cancers in people with HIV are associated with an oncogenic virus infection
 - Kaposi's Sarcoma – HHV8
 - Hodgkin's Lymphoma / NHL – EBV
 - Cervical/Anal/Oropharyngeal – HPV
 - Liver Cancer – Hepatitis B and C
 - **EXCEPTION: Lung Cancer**
- Patients often present at younger age with more advanced disease
- High proportion of lung and anal cancers
 - Need for early diagnosis / prevention

ANCHOR Study

- Anal Cancer HSIL Outcomes Research
- Phase 3 trial across 25 US sites evaluating outcomes of high-grade squamous intraepithelial lesions in people with HIV
- Participants randomized to receive HSIL treatment or active monitoring
 - Treatment included ablative procedures, excision, or topical fluorouracil or imiquimod
- Rate of progression to cancer was significantly lower in the treatment group

The NEW ENGLAND JOURNAL of MEDICINE

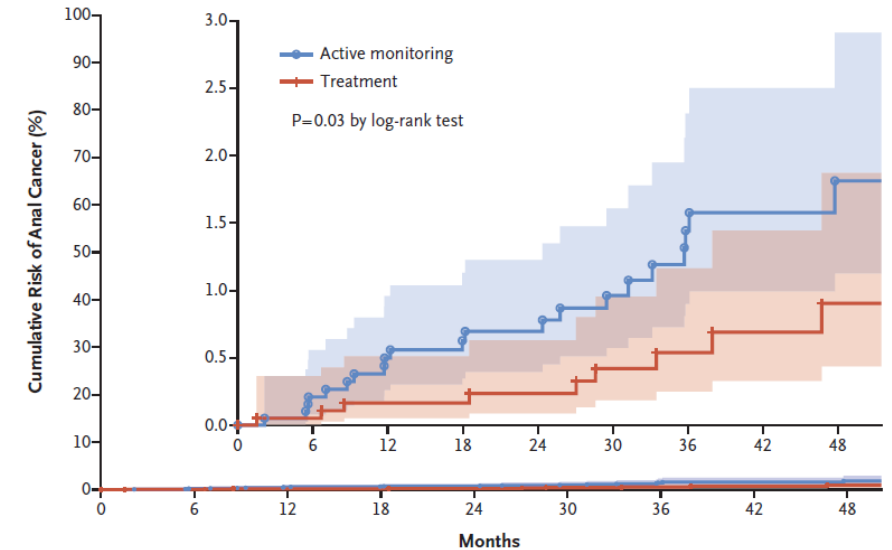
ORIGINAL ARTICLE

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulafia, J.T. Schouten, J. de la Ossa, R. Levine, J.D. Korman, M. Hagensee, T.M. Atkinson, M.H. Einstein, B.M. Cracchiolo, D. Wiley, G.B. Ellsworth, C. Brickman, and J.M. Berry-Lawhorn, for the ANCHOR Investigators Group*

ANCHOR Study

- Rate of progression to anal cancer was 57% lower in the treatment group
- Study discontinued early when data became clear that treatment of HSIL significantly reduced the risk of anal cancer



No. at Risk									
Active monitoring	2219	1856	1671	1459	1238	992	758	572	407
Treatment	2227	1871	1655	1473	1224	989	753	557	409

Figure 2. Kaplan–Meier Curve of the Time to Progression to Anal Cancer.

The inset shows the data on an expanded y axis. The shaded areas represent 95% confidence intervals.

ANCHOR Study

Additional research still needed to identify appropriate screening modalities for anal cancer

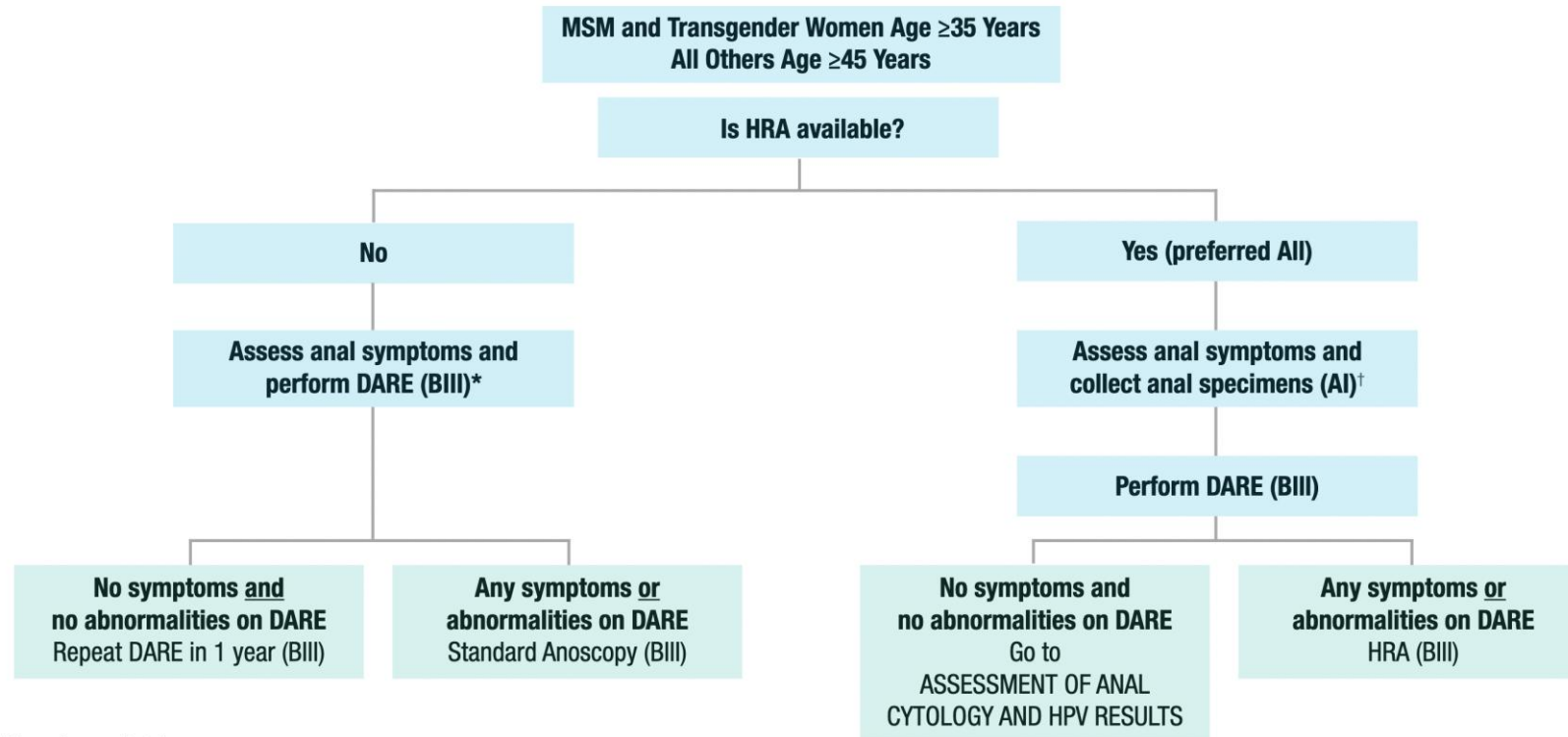
- High-resolution anoscopy is not feasible screening tools given high cost and limited availability
- Anal cytologic analysis and anal HPV testing have limitations

Not all anal cancers were prevented through HSIL treatment

- Larger lesion size associated with increased progression
- Often a large lesion burden and number in patients with HIV

Anal Cancer Screening Recommendations

SCREENING ALGORITHM FOR ANAL CANCER IN ASYMPTOMATIC PEOPLE WITH HIV



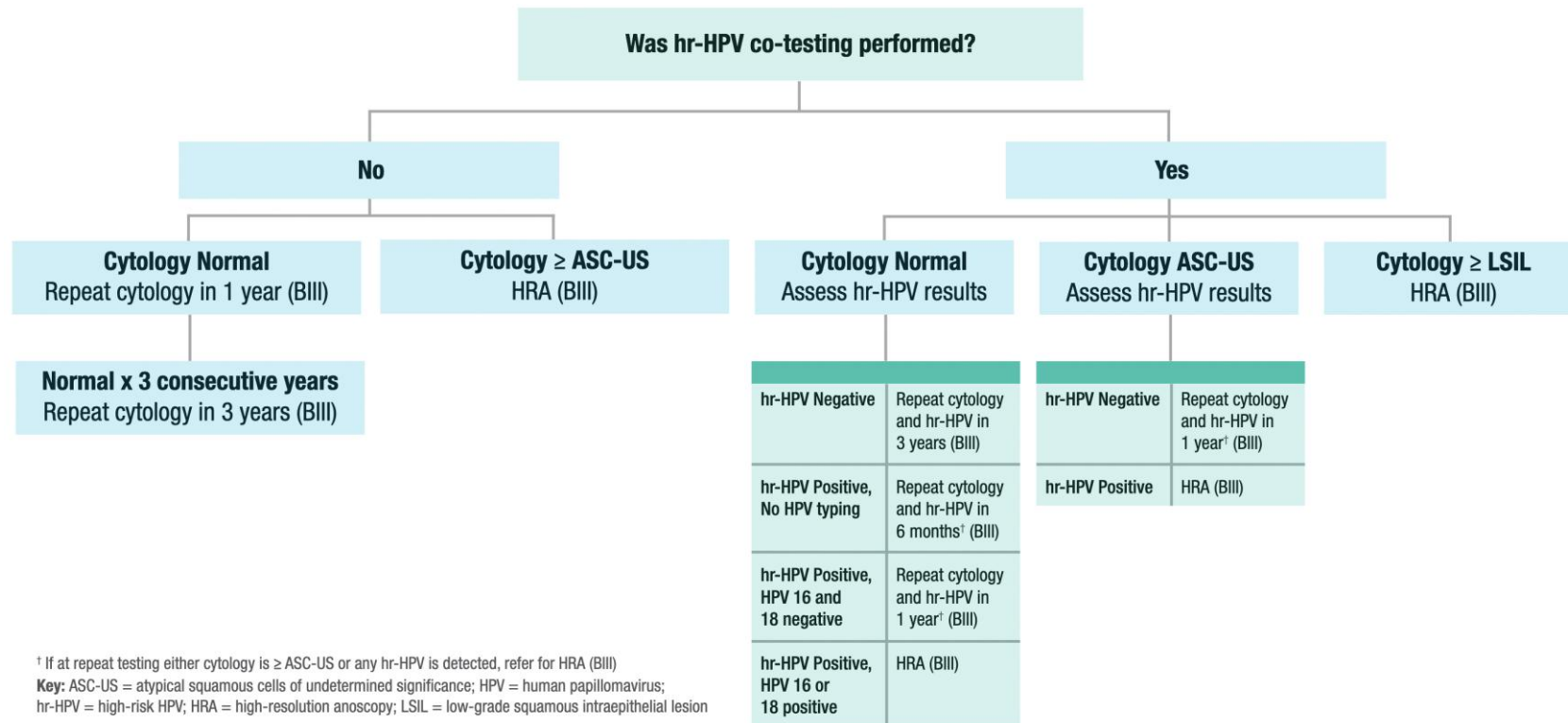
* No specimens collected

† Collect any specimens either for cytology or for cytology with HPV co-testing prior to DARE. HPV testing without cytology is not recommended (BIII)

Key: DARE = digital anorectal exam; HPV = human papillomavirus; hr-HPV = high-risk HPV; HRA = high-resolution anoscopy; MSM = men who have sex with men

Anal Cancer Screening Recommendations

ASSESSMENT OF ANAL CYTOLOGY AND HPV RESULTS IN PEOPLE WITH HIV

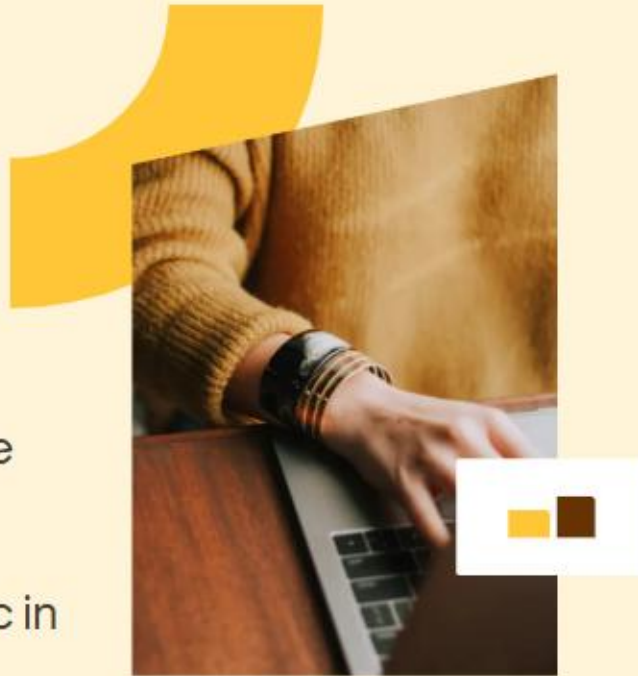


Case 3.

- 50-year-old gentleman presents to clinic for follow-up of his HIV infection
 - Originally diagnosed in 20 years earlier with a primary risk factor of men who have sex with men
 - On long-standing ART with perfect adherence
 - Undetectable HIV viral load and preserved CD4 count
- Has chronic headaches, which have been stable
- Requests neuropsychiatric testing for insurance/disability assessment, but denies any complaints

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Case 3.

Neuropsychiatric testing performed

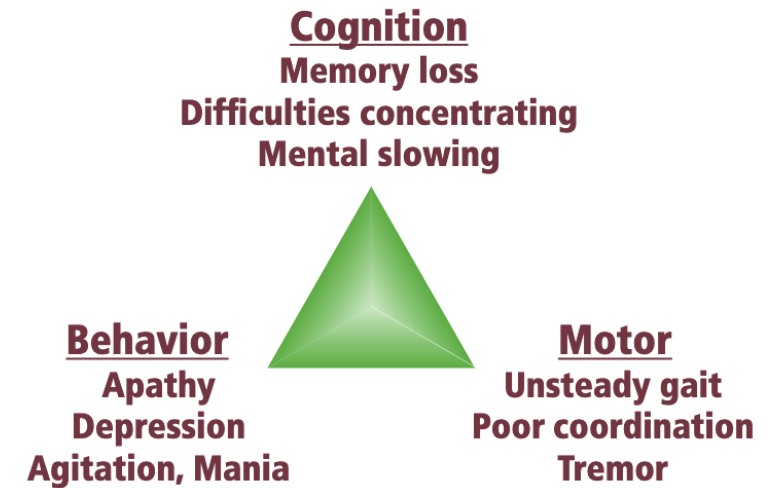
- Reveal significant cognitive deficits
- Problems with attention, psychomotor integration, executive function, and memory
- Retrieval based memory impairment is prominent
- Meets criteria for major neurocognitive disorder
- Patient has reduced insight into level of impairment and functionality

Neurocognitive Impairment and HIV

- Cognitive impairment has been a common complication of HIV infection since its discovery
- Pre-ART
 - AIDS dementia complex seen in people with advanced immunodeficiency
- ART Era
 - HIV-associated neurocognitive disorder (HAND) has decreased to < 5% of individuals on ART
 - Milder forms of neurocognitive impairment are common
 - Based on studies in younger individuals

Neurocognitive Impairment and HIV

- HIV enters the CNS within days of infection
 - Impaired cognition and depression are frequent symptoms following new infection
- Without ART, cognitive problems will develop and progress
 - Affect psychomotor speed, information processing, executive function, and working memory



Chan et al. 2021. Topics in Antiviral Medicine

Neurocognitive Impairment and HIV

Challenges facing older people with HIV

- Co-occurrence of other causes of cognitive impairment
- Possibility that HIV infection accelerates cognitive aging
- Unknown how HAND and other causes of cognitive impairment impact each other
- Cognitive screening tools used for common neurodegenerative diseases may not perform the same in people with HIV

Case 4

- 59-year-old female presents to clinic for follow-up of HIV infection
- She was initially diagnosed in 2001 and has been on treatment since that time.
- Her current regimen is:
 - **Tenofovir (TDF)/Emtricitabine Plus Dolutegravir (Truvada, Tivicay)**
- She has excellent adherence and has maintained viral suppression and a good CD4 count since the time of diagnosis
- Other past medical history includes hypertension, hyperlipidemia, and Type 2 diabetes.
- She has no prior history of opportunistic infections

Case 4

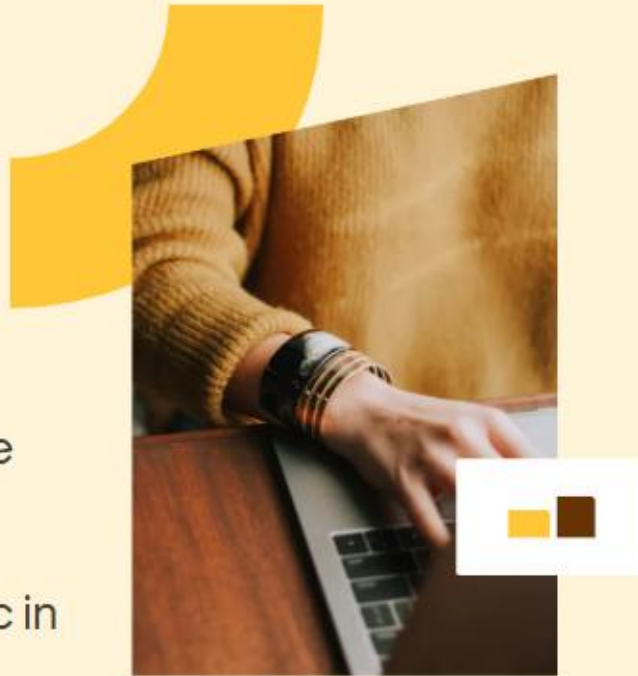
- Laboratory studies today show:

Test	Result
WBC	6.1
Hemoglobin	13.7
Platelets	245
Sodium	138
Potassium	4.8
Bicarbonate	22
BUN	32
Creatinine	1.9
GFR	42

Test	Result
AST	28
ALT	25
HA1C	8.1
Urinalysis	1+ Protein
CD4	610
HIV Viral Load	Undetectable

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Impact of HIV and Kidney Disease

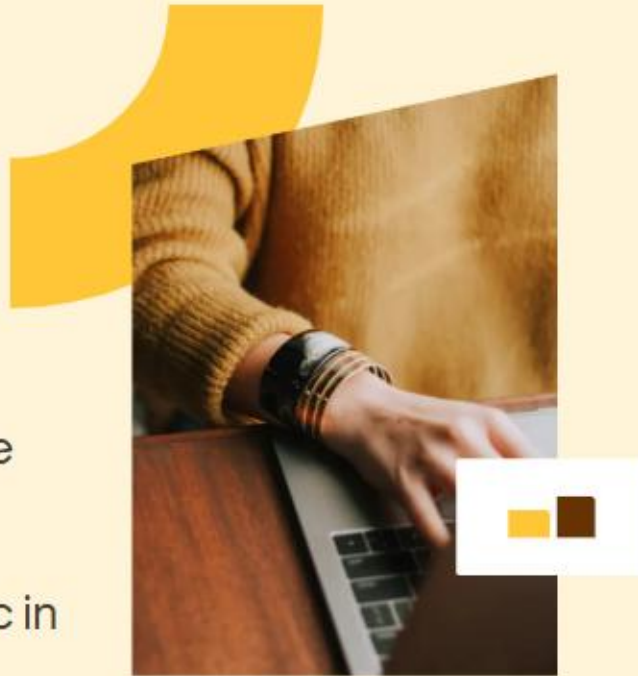
- There is decline in renal function that occurs with aging
 - 50% of adults over age 70 have a GFR <60 ml/min
- In the AgeHIV cohort study, there was a higher prevalence and faster progression of CKD among people with HIV compared to those without
- HIV-Associated Nephropathy (HIVAN)
 - Rapidly progressive kidney failure and severe proteinuria in the setting of untreated HIV infection

HIV Medications and Kidney Disease

- Nephrotoxicity of antiretroviral therapy
 - Proximal tubular injury can occur with use of tenofovir disoproxil fumarate (TDF)
 - Characterized by glycosuria, proteinuria, phosphate wasting, and decreased GFR
 - Tenofovir alafenamide (TAF) now preferentially used in individuals with HIV
- Other medications can block tubular secretion of creatinine
 - Integrase inhibitors
 - Trimethoprim-sulfamethoxazole

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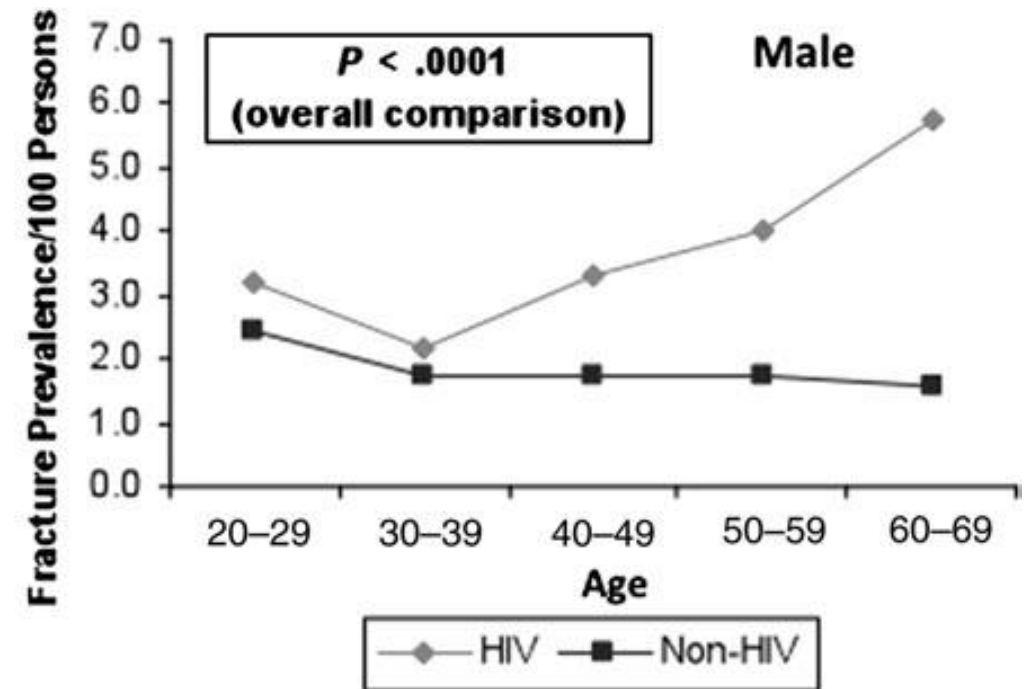
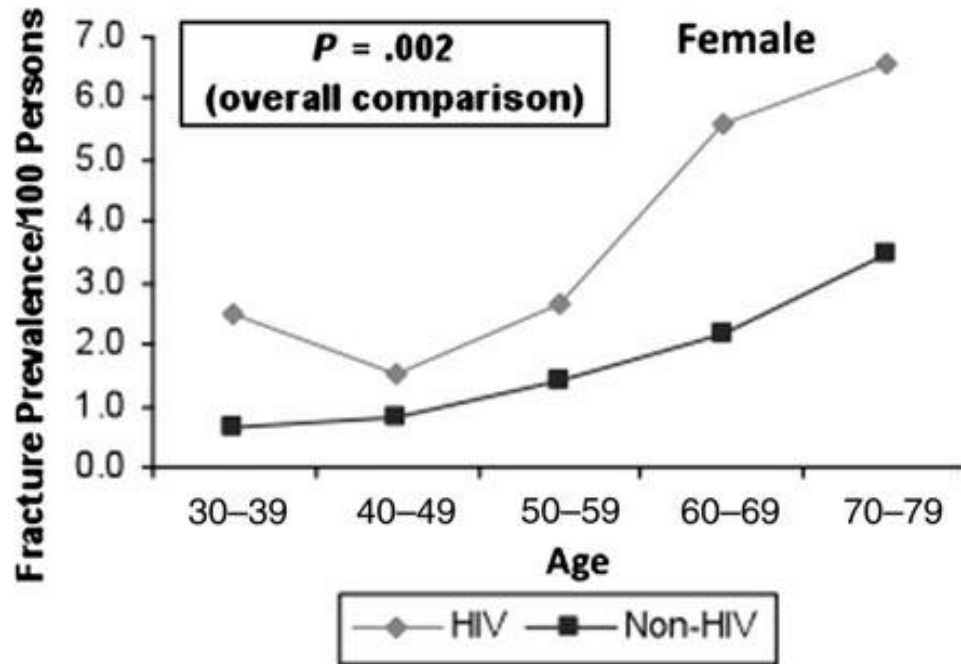
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HIV and Bone Disease

- People with HIV have an increased risk of low bone mineral density and fragility fractures
 - Increased prevalence of risk factors
 - Poor nutrition
 - Low body weight
 - Tobacco and alcohol use
 - Low vitamin D levels
- Osteoporosis may be associated with significant long-term morbidity, and is likely to increase as the population ages

Young et al. Clinical Infectious Diseases. 2011.
Pramukti et al. PLoS One. 2020
Chang et al. Archives of Osteoporosis. 2021

HIV and Bone Disease



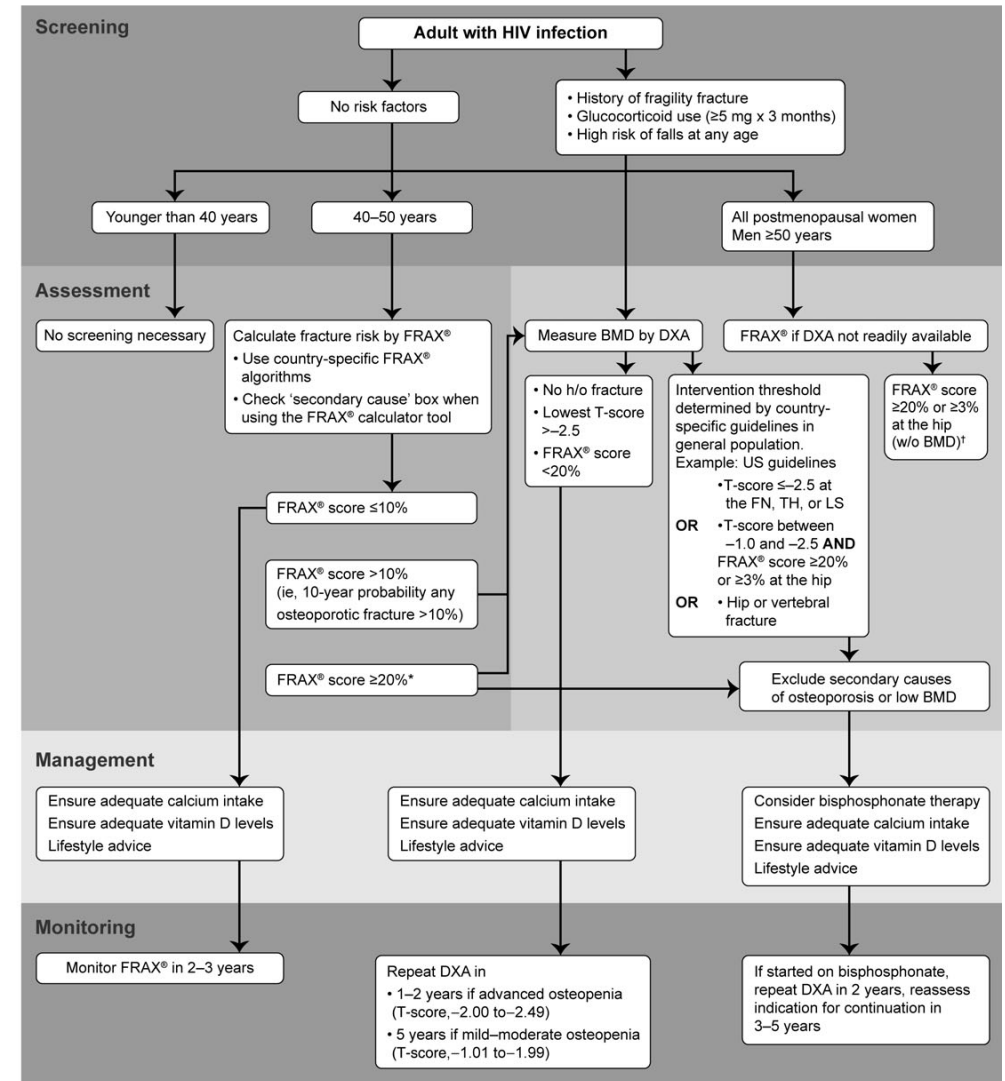
HIV and Bone Disease

- Direct Viral and Inflammatory Effects
 - Bone resorption and bone formation are uncoupled
 - Viral proteins stimulated osteoclast activity (Vpr, gp120)
 - Viral proteins also suppress osteoblast activity and stimulate osteoblast apoptosis (p55-gag)
 - Inflammatory cytokines promote osteoclastogenesis and bone resorption
 - May be exacerbated by high viral loads
- Antiretroviral therapy
 - Cumulative exposure to boosted PI associated with increased fracture risk
 - Tenofovir associated with decreased density in the hip and spine
 - Impairs bone mineralization through effects on renal phosphate handling

HIV and Bone Disease

■ Screening Recommendations:

- Screen all HIV-infected post-menopausal women and men ≥ 50 with DXA.
- Calculate FRAX score for patients between 40-50 years to determine need for screening.
- Screen all high-risk patients at any age:
 - - History of fragility fracture
 - - Glucocorticoid use
 - - High risk of falls

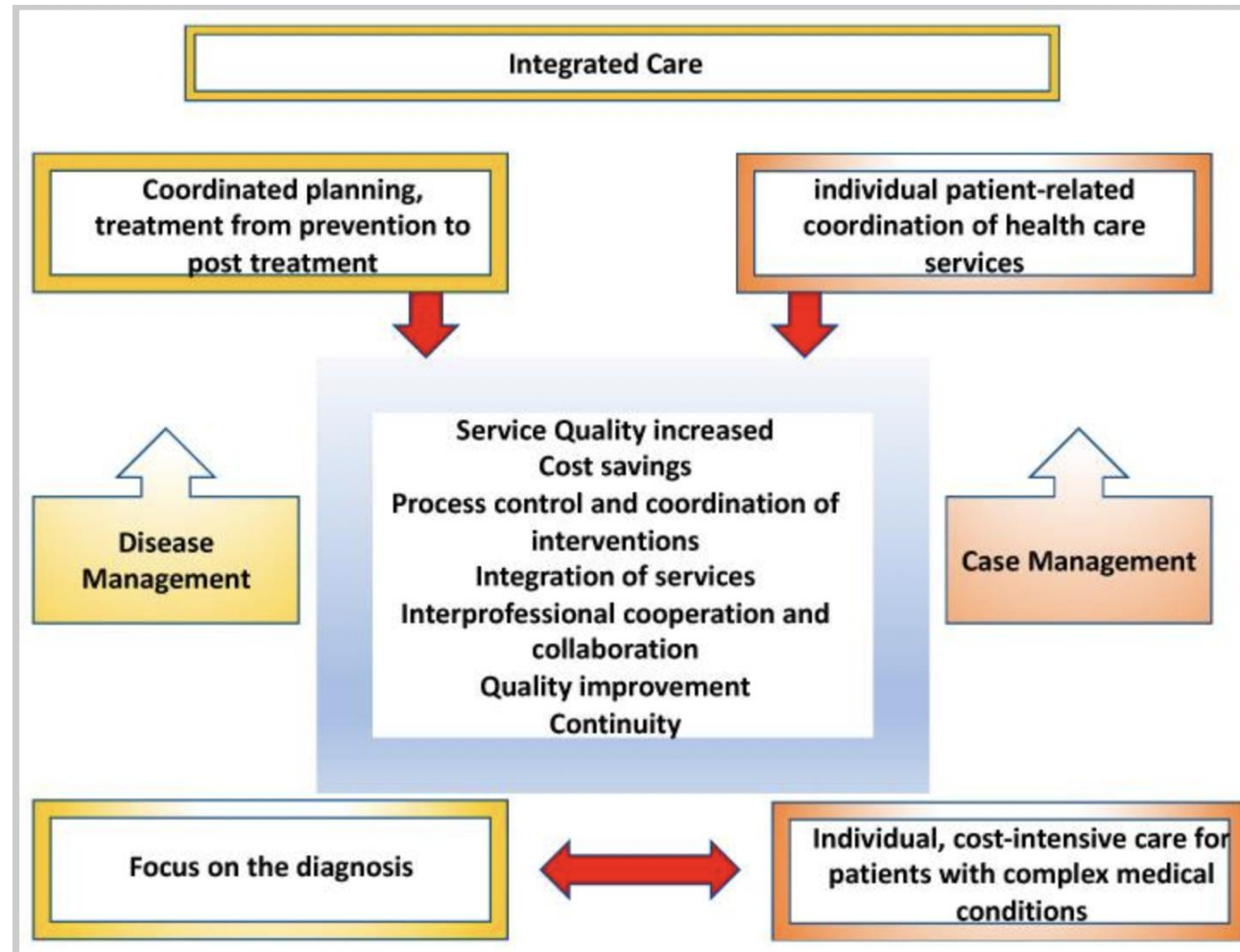


Integrated Care Approach

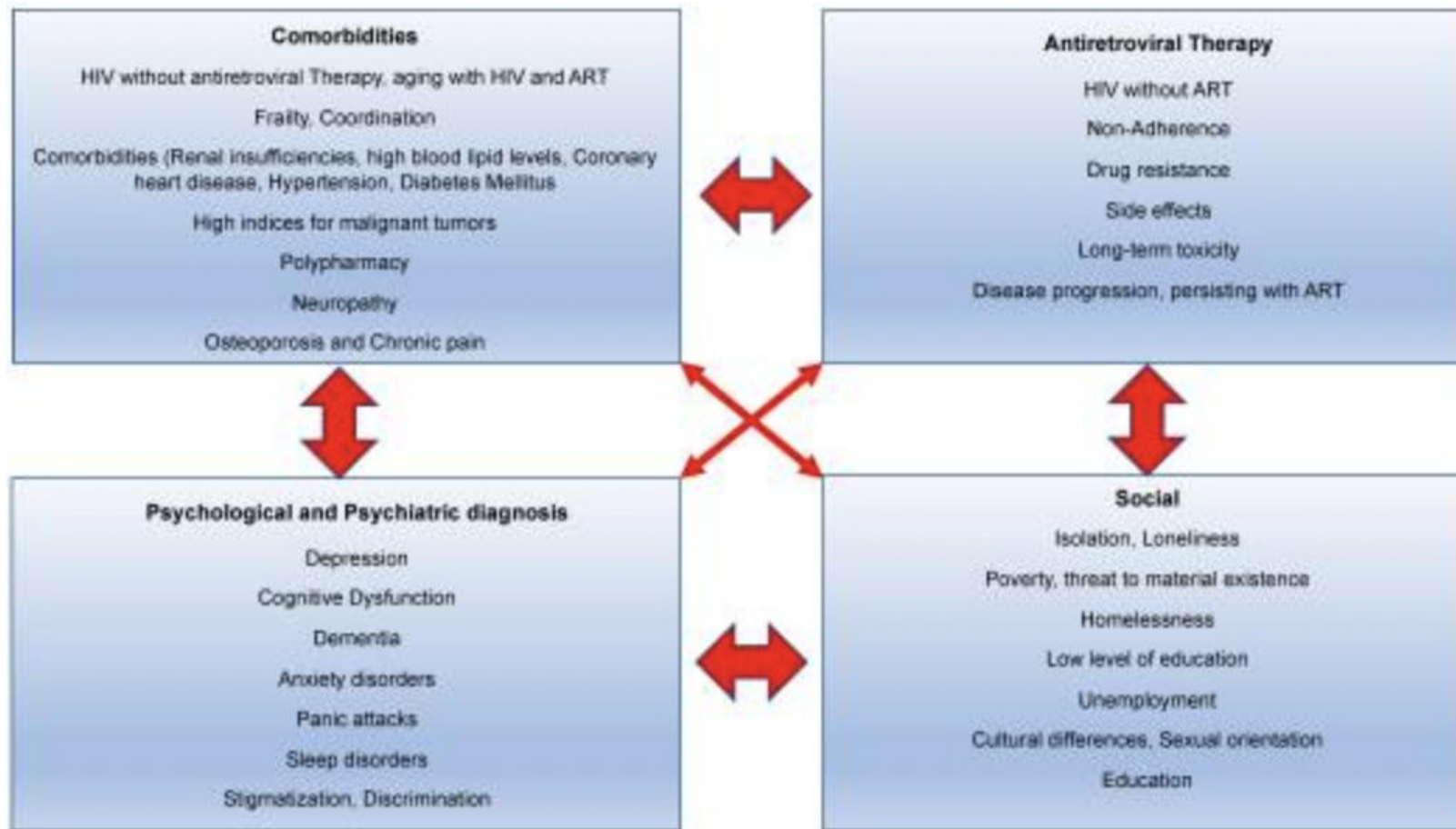
Integrated Care Model for People with HIV

- As the population of people with HIV continues to age and develop an increasing number of comorbid conditions, an integrated care model offers the most benefits for long-term health
- Integrated care considers medical, nursing, psychosocial, and psychiatric needs as well as the various interactions among them.
- This interprofessional care approach helps maintain evidence-based care and manage comorbidities and polypharmacy.

Integrated Care Model for People with HIV



Integrated Care Model for People with HIV



Summary

- In the era of ART, people with HIV are living longer, and the overall population is getting older
- Older patients with HIV have high rates of comorbid conditions and frailty, likely related to chronic immune activation and potentially accelerated aging
- Research into the best strategies to screen and manage comorbid conditions in older people with HIV is still ongoing.
- An integrated care model can assist patients who are aging with HIV infection and improve overall health by taking a holistic patient centered approach.

On Being the First Generation to Face the Aging Process with HIV

“For somebody like myself there isn’t really anybody about who has lived longer with the virus. So I am part of a generation who are finding out precisely what the correlation between health, HIV, age, sexuality. It’s still in the test tube and finding out how the experiment ends...”

Research Participant – Age 56



AGE IS NOT A CONDOM.
Americans aged 50 and older have many of the same HIV risk factors as younger Americans. Educate yourself. Get tested for HIV.

Find HIV Testing Near You:

- Send a text message with your ZIP code to KNOWIT (568948)
- Visit gettested.cdc.gov
- Visit locator.aids.gov
- Contact 1-800-CDC-INFO (1-800-232-4636)

National HIV/AIDS and Aging Awareness Day
September 18th
Visit www.NHAAD.org for more information.



SEPTEMBER 18

**NATIONAL
HIV/AIDS
AND AGING
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  Ending the HIV Epidemic

THANK YOU SO MUCH

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