



# BHIVA 'Best of CROI' feedback webinars 2024

Co-morbidities and ageing  
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*This educational event is supported by*



*With thanks to those presenting research for permission to use slides for 'Best of CROI'*



## **Conflict of Interest**

Caroline Sabin has received financial support for the membership of Data Safety and Monitoring Boards, Advisory Panels and for preparation of educational materials from Gilead Sciences, ViiV Healthcare and MSD.

# Topics to be covered

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- REPRIEVE – the follow-up studies
- Other updates on CVD and diabetes
- Cognitive function
- Mental health and ageing



# The REPRIEVE trial



- Main study<sup>1</sup> demonstrated 35% reduction in hazard of major adverse cardiovascular event\* (MACE) in those receiving pitavastatin vs placebo

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### BHIVA rapid guidance on the use of statins for primary prevention of cardiovascular disease in people living with HIV

In cohort studies, compared to the general population or controls without HIV, people living with HIV are at greater risk of atherosclerotic cardiovascular disease (CVD). There are established national guidelines for the primary prevention of CVD with statins. Because general population CVD risk calculators may underestimate risk in people living with HIV, HIV is considered an additional CVD risk factor, but there are no specific recommendations for people living with HIV. REPRIEVE, the largest randomised trial undertaken in people living with HIV, demonstrated a significant reduction in major adverse cardiovascular events in participants randomly assigned to pitavastatin 4 mg daily as compared to those receiving placebo. Here we provide rapid guidance on the implications of the REPRIEVE study for clinical practice. Statins are an effective tool to reduce CVD risk but should be considered in the context of holistic lifestyle optimisation with a particular focus on smoking cessation. While current guidelines in primary prevention focus on estimated 10-year CVD risk, the goal of this guidance is to attenuate lifetime not just 10-year risk.

This guidance was released in November 2023 and will be reviewed in November 2024.

### Updates HIV Clinical Guidelines: Adult and Adolescent ARV

**Date:** February 27, 2024

**Source** ClinicalInfo

The Department of Health and Human Services Guidelines Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (the Panel) has developed recommendations for the use of statin therapy in people with HIV, in collaboration with representatives from the American College of Cardiology (ACC), the American Heart Association (AHA), and the HIV Medicine Association.

<sup>1</sup>Grinspoon SK et al. NEJM 2023; 389:687-699

\*CV death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause

# The REPRIEVE trial – mechanistic insights (1)

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- Mechanistic sub-study: pitavastatin associated with significant reduction in progression of non-calcified plaque volume (NCPvol) and reductions in oxLDL and Lp-PLA2
- Current analysis: 563 participants in plaque substudy
- No associations between changes in Lp-PLA2, oxLDL, hsCRP or LDL, and NCPvol
- Adjustment for changes in biomarkers did not impact the effect of pitavastatin to reduce NCPvol

## The REPRIEVE trial – mechanistic insights (2)

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- Targeted proteomics of biological pathways mediating statin effects on NCPvol in 542 participants who continued assigned treatment for 2 years
- Pitavastatin associated with:
  - ↑ expression of PCOLCE, NRP-1, MIC-A/B
  - ↓ expression of TFPI, TRAIL, ANGPTL3, MBL2
- Pitavastatin resulted in 26% ↑ in PCOLCE
- Each 1-fold ↑ PCOLCE associated with 25% ↓ in NCPvol
- 93% of NCPvol reduction was mediated through pitavastatin effects on PCOLCE

# The REPRIEVE trial – risk factors for MACE (n=7769)

- Risk for first MACE higher for:
  - age 50-59 and  $\geq 60$  vs. 40-49 (HRs: 1.98 and 2.11)
  - family history of premature CVD (HR:1.57)
  - Black/African American (vs. white, within HIC HR: 1.75)
  - current/former smokers (HR: 1.66),
  - HTN (HR: 1.68)
  - detectable VL (HR 1.46)
  - lower HDL-C (HR 0.83)
- Higher risk of MACE among those from HIC vs. most other regions
- No significant effects of female sex, BMI, glucose, eGFR, or nadir CD4 after adjustment

# The REPRIEVE trial – performance of ACC/AHA PCE

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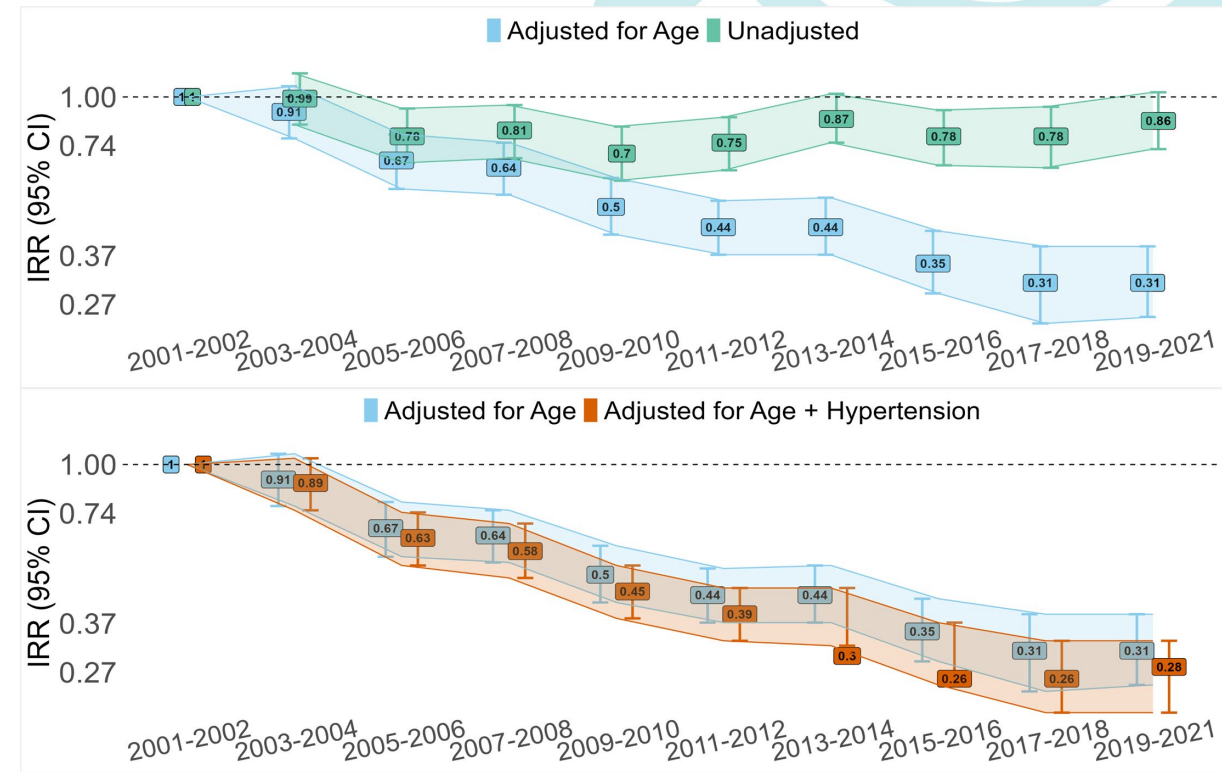
- Outcomes: CV death, MI, stroke
- Overall discrimination good (C statistic 0.72) but:
  - Under-prediction in HIC
  - Over-prediction in LMIC
  - Under-prediction in women and BA participants in HIC
- PCE based on systematic review of evidence from pre-statin era
  - ARIC, CHS, CARDIA, Framingham and Framingham Offspring studies
  - Widely reported to over-estimate risk





# CVD and diabetes – D:A:D/RESPOND

- Temporal trends of CVD incidence, 2001-2021
- Drop in age-adjusted incidence of CVD over time
- Did not seem to be driven by changes in most CVD risk factors, although an increasing prevalence of hypertension in later years may have reduced the size of the drop



# CVD and diabetes – Johns Hopkins cohort



- People with HIV aged >18 years without diabetes who had used NNRTI or PI for  $\geq 180$  days and had visited 2007-2023
  - median age 50, 65% male, 76% Black American, 59% with overweight or obesity
- Emulated trial of switching to INSTI vs continuing on NNRTI or PI
- HR (95% CI) for incident diabetes:

Overall	1.22 (0.85, 1.74)
<u>Time since switch</u>	
$\leq 2$ years	2.79 (1.83, 4.26)
$> 2$ years	0.80 (0.49, 1.29)

# Cognitive function - CONNECT study, South Africa

- 178 people with HIV, virally suppressed on EFV, switched to DTG
  - 145 followed one year later
- 95 socio-demographically similar people without HIV
  - 40 followed at 1 year

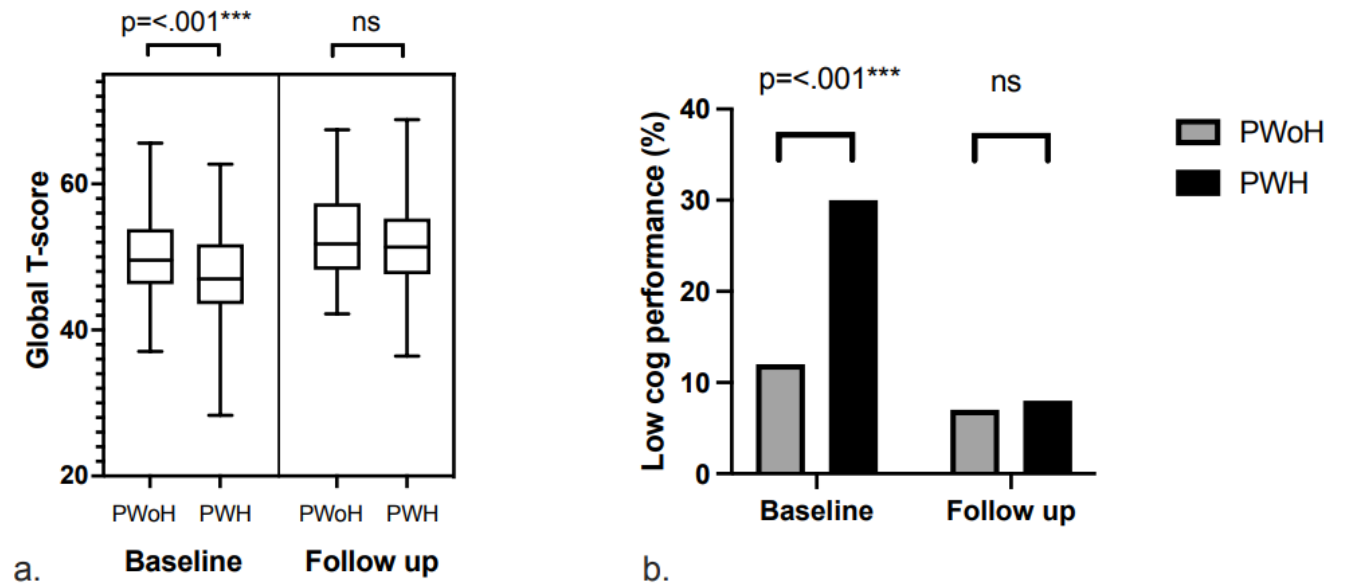
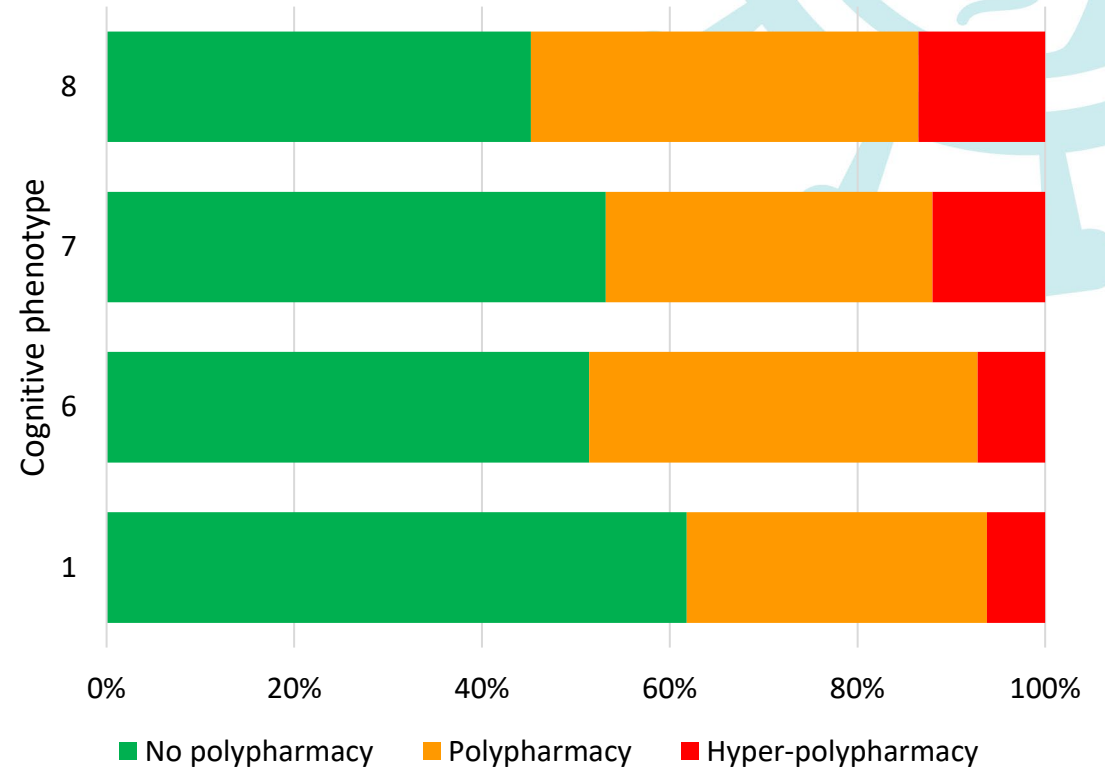


Figure 1. Cognitive performance by a) global T-score and b) GDS at baseline (EFV) and follow up (DTG). Improvements in PwOH over time relate to practice effects.

# Cognitive phenotype and polypharmacy - ACTG A5322

- 8 cognitive phenotypes (1=best)
- N=870 people with HIV
  - 18.4% female, 52.2% non-white
- Polypharmacy (>5 drugs) and hyper-polypharmacy (>10 drugs) both more common in those with poorer cognitive function



# Cognitive function – Washington Uni, St. Louis

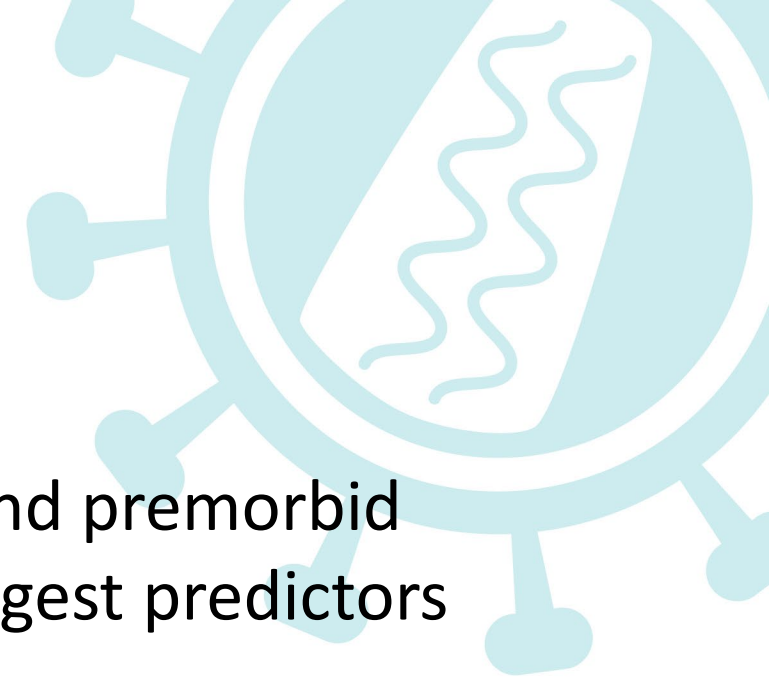
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<sup>1</sup>n=225 people with HIV

- Sociodemographic factors (particularly education and premorbid IQ), not clinical or neurological features, were strongest predictors of cognitive profiles

<sup>2</sup>n=227 with HIV, n=107 without HIV

- Greater recent exposure to air pollutants associated with worse cognition and changes to plasma markers of inflammation and neurodegeneration in those with HIV



# Depression and mental health

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- CEFAR Network of Integrated Clinical Systems (CNICS) cohort
- 2,040 people with HIV and DM followed for median of 2.9 years<sup>1</sup>
  - Diagnosed depression was common (56%)
  - Higher depressive symptom burden associated with poor DM control but association differed by ethnicity
- 13,817 people with HIV followed for mean of 7.6 years<sup>2</sup>
  - Time-varying depressive symptom severity (/5 pt higher PHQ-9 score) associated with higher stroke risk (aHR 1.16)
  - Greater impact in those aged <50 years but no difference by sex
  - New onset depressive symptoms associated with highest stroke risk

<sup>1</sup>Ahonkhai AA, et al. Abstract 833; <sup>2</sup>Ma J, et al. Abstract 110

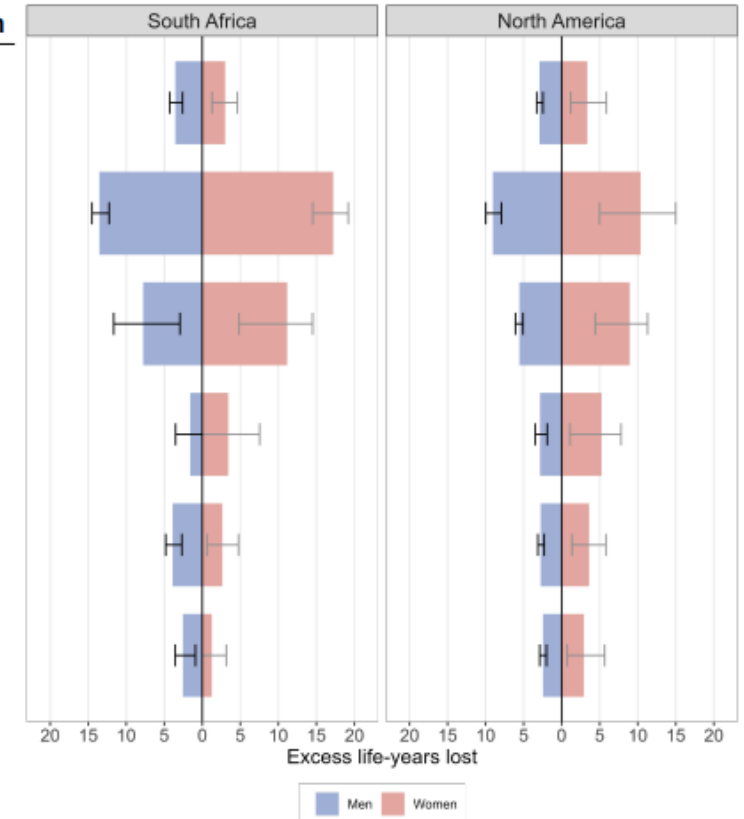
# Life-years lost due to mental illness, S Africa & N. America

- People with HIV and mental health diagnoses die 1 to 17 years earlier compared to people with HIV without any mental health diagnosis

Proportion with a diagnosis of mental illness

	South Africa		North America	
	Men	Women	Men	Women
<b>Any mental illness (F00-F99*)</b>	44.9%	50.4%	62.8%	65.4%
<b>Organic disorder (F00-F09)</b>	1.7%	1.1%	1.6%	1.8%
<b>Psychotic disorder (F20-F29)</b>	1.0%	0.9%	12.7%	10.2%
<b>Bipolar disorder (F31)</b>	2.1%	2.7%	9.4%	12.3%
<b>Depression (F32, F33, F34.1)</b>	23.8%	29.6%	50.8%	55.1%
<b>Anxiety disorder (F40-F49)</b>	30.4%	37.0%	43.8%	40.0%

All-cause excess life-years lost



\*Excluding F10-F19 (substance use disorder)

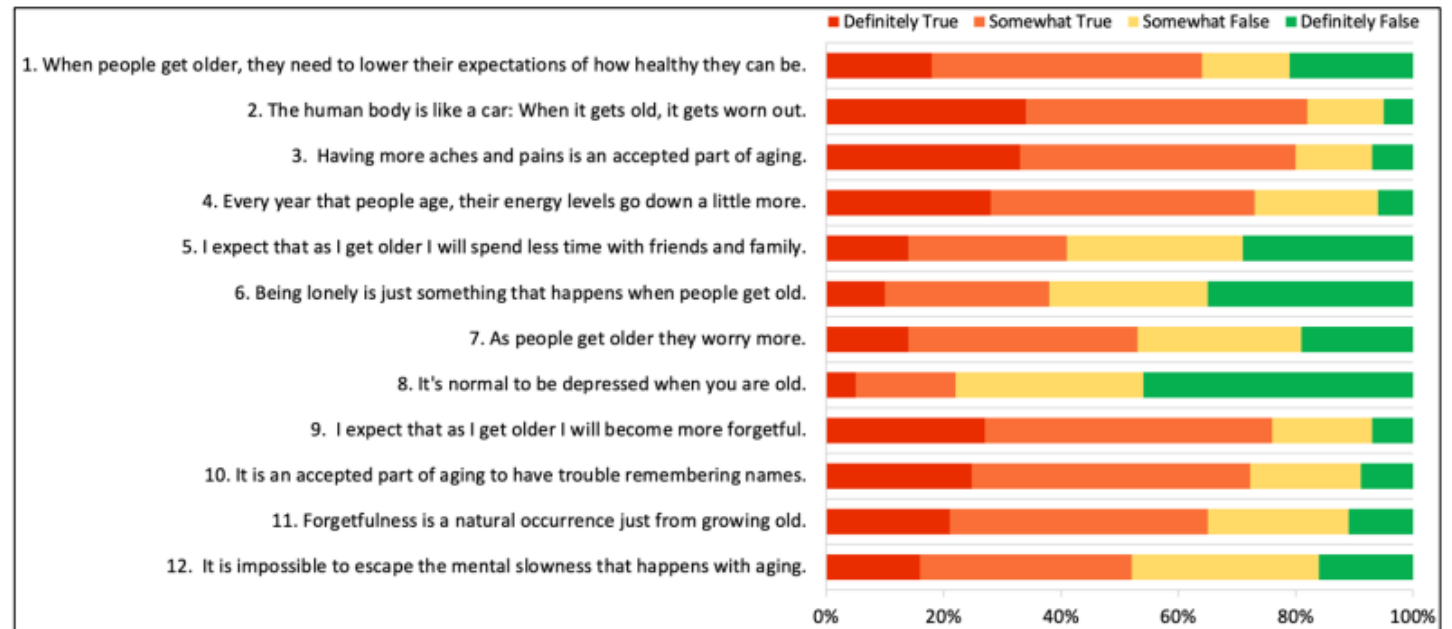
Figure: Proportion of people with HIV with a diagnosis of mental illness (left, ICD-10 codes in parentheses) and all-cause excess life-years lost associated with mental illness with 95% confidence intervals (right), by gender and region.



# Perceptions of ageing

- 320 participants in the Correlates of Healthy Aging in Geriatric HIV (CHANGE HIV) study
- 91% men, 78% white, median age 69 years
- Lower expectations of aging in women, those with depression, and those with greater social isolation

Figure 1. Expectations Regarding Aging Survey results among persons living with HIV age 65 and older.



Questions 1-4 correspond to physical health, 5-8 correspond to mental health and 9-12 correspond to cognitive function domains.



# Take home messages

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- Clarification on the impact of statins on CVD in people with HIV
  - Standard CVD risk factors generally continue to predict risk in people with HIV
  - CVD risk equations developed/validated in the US don't always predict well in other settings
- Greater appreciation of the role of socio-economic and other non-HIV factors in the development of comorbidities and cognitive health
- Appreciation of the importance of interventions to support both physical and mental health as people with HIV age

