Title
Delayed presentation of HIV among older individuals: a growing problem

Journal
The Lancet HIV, 9(4)

ISSN
2405-4704

Authors
Justice, Amy C
Goetz, Matthew B
Stewart, Cameron N
et al.

Publication Date
2022-04-01

DOI
10.1016/s2352-3018(22)00003-0

Peer reviewed

Delayed Presentation of HIV Among Older Individuals: A Growing Problem

NA-ACCORD

- Amy C Justice, MD, PhD
  - VA Connecticut Healthcare System, Yale Schools of Medicine and Public Health
  - Amy.Justice2@va.gov
  - 0000-0003-0139-5502
  - Yale University
  - USA
- Keri N Althoff, PhD, MPH
  - Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
  - kalthoff@jhu.edu
  - 0000-0002-5068-6595
  - Johns Hopkins University
  - USA
- Cameron N Stewart, MS
  - Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
  - cameron.stewart@jhu.edu
  - 0000-0002-9982-5808
  - Johns Hopkins University
  - USA
- Brenna C Hogan, MPH
  - Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
  - bhogan7@jhu.edu
  - 0000-0002-7100-8910
  - Johns Hopkins University
  - USA
- Elizabeth Humes, MPH
  - Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
  - ehumes1@jhu.edu
  - 0000-0003-3432-7688
  - Johns Hopkins University
  - USA
- Matthew B Goetz, MD
  - VA Greater Los Angeles Healthcare System
  - Matthew.goetz@va.gov
  - 0000-0003-4542-992X
  - David Geffen School of Medicine at UCLA
  - USA

CCASANet

- Paula M Luz, MD, PhD
  - Affiliation Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz
  - luzpaulamendes@gmail.com
  - 0000-0001-9746-719X
  - Fundação Oswaldo Cruz
  - Brazil
- Jessica Castilho, MD, MPH
  - Division of Infectious Diseases, Department of Medicine
  - jessica.castilho@vumc.org
  - 0000-0002-7599-8173
  - Vanderbilt University Medical Center
  - USA

Central Africa

- Denis Nash, PhD, MPH
  - City University of New York Department of Epidemiology and Biostatistics, Graduate School of Public Health and Health Policy
  - Denis.Nash@sph.cuny.edu
  - 0000-0002-3280-5386
  - City University of New York
  - USA
- Ellen Brazier, MA, MS
  - CUNY Institute for Implementation Science in Population Health
  - Ellen.Brazier@sph.cuny.edu
  - 0000-0002-8514-1958
  - City University of New York
  - USA

East Africa

- Beverly Musick, MS
  - Department of Biostatistics and Health Data Science, School of Medicine
  - bsmusick@iu.edu
  - 0000-0003-0334-6798
  - Indiana University
  - USA
- Constantine Yiannoutsos, PhD
  - Department of Biostatistics, Richard M Fairbanks School of Public Health
  - cyiannou@iupui.edu
  - 0000-0001-9014-3651
  - Indiana University
  - USA

West Africa

- Karen Malateste, Mstat
  - Inserm, French National Research Institute for Sustainable Development (IRD), UMR 1219
  - Karen.Malateste@u-bordeaux.fr
  - 0000-0003-1568-353X
  - Universite de Bordeaux
  - France
- Antoine Jaquet, MD, PhD
  - Inserm, French National Research Institute for Sustainable Development (IRD), UMR 1219
  - antoine.jaquet@u-bordeaux.fr
  - 0000-0002-3426-9492
  - Universite de Bordeaux
  - France

Southern Africa

- Morna Cornell, PhD, MPH
  - Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, Faculty of Health Sciences
  - morna.cornell@uct.ac.za
  - 0000-0001-7149-8799
  - University of Cape Town
  - South Africa
- Tinei Shamu, HBMLS, MPhil
  - Newlands Clinic
  - tineis@newlandsclinic.org.zw
  - 0000-0001-8931-4484
  - Graduate School of Health Sciences and Institute of Social and Preventative Medicine, University of Bern, Switzerland
  - Zimbabwe

Asia Pacific

- Reena Rajasuriar MPharm, PhD
  - Department of Medicine, University of Malaya
  - reena@ummc.edu.my
  - 0000-0003-3756-0629
  - University of Malaya
  - Malaysia

- Awachana Jiamsakul, Mstat, PhD
  - Biostatistics and Databases Program
  - ajiamsakul@kirby.unsw.edu.au
  - 0000-0003-4810-0783

- The Kirby Institute, UNSW Sydney
- Australia

Summary

Late presentation for care is a major impediment to prevention and effective treatment of HIV infection. Older individuals are at increased risk for late presentation, represent a growing proportion of all those with late presentation, and may require interventions tailored to their age group. We provide a summary of the worldwide literature published between 2016-21 (reporting data from 1984-2018) quantifying the association of age with delayed presentation. Using the most common definitions of late presentation and older age from these earlier studies, we update this work with data from the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium focusing on data from 2000 to 2019 encompassing 4 continents. Finally, we consider how late presentation among older individuals might be more effectively addressed as electronic medical records become widely adopted.

Key Messages

- Late presentation for HIV care is a major impediment to prevention and effective treatment of HIV infection.
- A growing proportion of adults presenting for HIV care are ≥50-years-old and nearly half of them have delayed presentation.
- In many regions of the world, the age associated gap in CD4 cell count at presentation is widening as the average CD4 cell count at presentation rises faster for younger adults.
- Few studies have focused on specific factors associated with late presentation for older adults.
- Early diagnosis and treatment of HIV for older individuals is particularly challenging because early signs and symptoms may be attributed to diseases of aging and because neither these individuals nor their care providers perceive them to be at risk for HIV.
- If the widening age associated CD4 gap is to be addressed, interventions will need to be explicitly targeted to older individuals.

Introduction

The successful scale-up of effective antiretroviral therapy (ART) has supported the long-term survival of people with HIV infection (PWH). More people are living with HIV than ever before and this population is aging(1-4). Globally, between 2015 and 2020, UNAIDS estimated that the total number of PWH over the age of 50 years increased from 5.4 million to 8.1 million (aidsinfo.unaids.org). In this four-part series co-sponsored by *The Lancet HIV* and *The Lancet Healthy Longevity*, we explore pressing issues facing those aging with HIV in the era of ART. In this article, we begin by addressing risk of delayed presentation for ART, subsequent articles consider 1) evidence for and against accentuated biologic ageing compared with people without HIV infection, 2) how health systems might adapt to an ageing population of PWH, and finally 3) the syndemic of stigma particular to those aging with HIV.

In many settings, as the prevalence of HIV among older individuals has grown the number of new infections in this age group has increased. For example, between 2015 and 2019 in the United States, the overall prevalence of PWH increased by 8% and incident infections decreased by 4%(5). In contrast, we saw a 40% increase (289,900 to 407,100) in prevalence and 15% increase (2700 to 3100) in incidence among those 50 years and older – the largest increases of any age group(5). This is likely due to intra-generational and cross generational unprotected sexual activity(6, 7).

Large scale population based statistics on HIV incidence in older age groups for other parts of the world are limited but some data is available from South Africa. By the end of 2013 , 14% (6304/44909) of PWH in care were ≥50 years(8). Among 84,078 patients starting antiretroviral therapy from 2004 to 2013, the proportion of

those ≥50 years increased from 6% (290/4999) in 2004 to 10% (961/9657) in 2012-13(8). Another study tested in 2010 and retested in 2015 a cohort of 1,360 individuals aged 40 or more years in 2015 (6). HIV prevalence increased from 21% to 23% corresponding to 33 incident infections (0.49 infections per 100 Person Years); only those 80 or more years of age experienced no new infections(6).

Twelve years ago, we used data from the United States and Canada to compare CD4 cell count and AIDS-defining conditions at presentation for HIV care among those under 50 and those 50 years of age and older(9). Older individuals had lower CD4 cell counts and a higher prevalence of AIDS-defining conditions at diagnosis, and these gaps between younger and older at presentation persisted over calendar time despite decreases in new diagnoses among both groups(9). Now that an even larger proportion of individuals living with HIV are 50 years and older worldwide, we revisit the relationship between age and delayed presentation for care globally with a review of recent literature, data analyses from the International epidemiology Databases to Evaluate AIDS (IeDEA) network, and a consideration of what might be done to decrease new HIV infections and delayed presentation for care among older individuals.

Review of Recent Literature (2016-2021)

We conducted a structured review of recent literature (see Search Strategy and **Table 1**)These studies were conducted in North and South America, Europe, Africa, Middle East, Asia, and Australia and include observations from 1984 through 2018. Most (32) defined late presentation as having a CD4 cell count of <350 cells/μL or an AIDS diagnoses at or near the time of presentation for care. Although these studies document improvements in recent years, delayed presentation

remains a significant global issue in HIV care. In many settings, approximately half of those newly diagnosed with HIV infection have CD4 counts below 350 cells/μL at presentation and the proportion is even higher in lower- and middle-income countries.

Older age was variably defined, sometimes as young as “35 years or older”, but older age (usually defined as ≥50-years-old) was consistently associated with delayed presentation. Relative risk (typically measured using adjusted odds ratios but in some cases we calculated unadjusted odds ratios from data provided) for delayed presentation associated with older compared to younger individuals (variably defined as <35 or <20 years) ranged from 1.1-7.4. The most common odds ratios were from 1.5-4.

Only one study that considered the role of age in late presentation concluded that older individuals were at decreased risk of late presentation for care. Gesewew et al. studied 4,900 people presenting for care at a single site in Southwestern Ethiopia and found that, compared to those 15-24 years of age, those 50 years and older were less likely to experience a delayed presentation (HR 0.4; 95% CI 0.3-0.6) (10). Another study conducted in Italy separated Italians from non-Italians and found that, compared to those 35-49 years of age, Italians 50 years of age were at increased risk (HR 1.5; 95% CI 1.4-1.7) but non-Italians 50 years of age were not (HR 0.9; 95% CI 0.7-1.2)(11).

Some of these studies considered whether there had been opportunities for earlier diagnosis and whether these differed by age(13-17). These opportunities were variably defined from as broad as “any prior medical encounter” to very specific as “diagnosis with an AIDS defining condition”. These studies documented more “missed opportunities” among older individuals.

IeDEA Data

To add a more recent and standardized accounting of delayed presentation for HIV care around the world, we have partnered with the International epidemiology Databases to Evaluate AIDS (IeDEA). IeDEA harmonizes data on care and treatment of people with HIV from seven international regional data centers including four in Africa, and one each in Asia-Pacific (which includes an Australia sub-cohort), Central/South America (also includes Mexico, Haiti, Honduras), and North America (United States and Canada). Each region contributed aggregated data from adults (≥18 years old) to the Epidemiology and Biostatistics Core of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), the North American region of IeDEA, where the figures presented were created. Cohorts in most regions have an ongoing process of adding all individuals presenting for HIV care, with the exception of cohorts in Southern Africa and the Asia Pacific. In the Southern African IeDEA region, participants enter into observation at ART initiation which may occur after presentation for HIV care; this region did not contribute to data visualizations of those presenting for HIV care. Asia-Pacific data combine two approaches to cohort enrollment – selectively enrolling patients to replace participants who died, were transferred, or were lost to follow-up (including all Australian sub-cohort sites), or enrolling all patients seen at the site. The results presented may not be representative of all persons in HIV care in the specified regions of the world as the IeDEA regional cohorts are observational and do not employ sampling strategies for representativeness. Additional information regarding selection of participants for enrollment into the IeDEA regional cohorts, the adoption of the Treat All guidelines, and the changes in CD4

testing that influence the results presented can be found in **Supplement Table 1** and a recent global IeDEA study (18).

Three study populations were defined. First, the population of individuals observed to present for HIV care at an IeDEA-contributing clinical care site was restricted to those who did not have prior evidence of an HIV care visit, a history of antiretroviral therapy, or a suppressed HIV viral load. Second, the population of individuals observed to be in HIV care in any calendar year from 2000 to the most recent data available for the region was restricted to those who were receiving ART, had a CD4 or HIV RNA measurement, or had evidence of an HIV care encounter. Third, the study population of individuals presenting for HIV care were further restricted to those who were observed to initiate ART at, or after, presentation for care.

Age was measured from year of birth. Sex was defined as sex at birth. The CD4 cell count closest to the date of presentation for HIV care measured within +/- 12 months and no more than 7 days after ART start was selected for this analysis. For the CD4 at ART initiation, we used a window of 12 months prior through 7 days post ART start to select the closest measurement for this analysis.

Histograms were created for each region to visualize the age distribution at presentation for care, and in the most recent complete calendar year of data available among those who were in HIV care. A kernel density smoothing bandwidth of 2.0 was used to visualize the age distribution histograms. We quantified the difference between the observed medians and the kernel density median estimate (which is not necessarily equivalent to the observed medians). Animated age distributions that visualize these changing age distributions over the last two decades can be found on the IeDEA YouTube Channel (iedea.org). The proportion of

adults presenting for HIV care was estimated within age groups (<50, 50-64, and 65+ years) among the total presenters for HIV care.

In 2013, the World Health Organization recommended viral load testing (and not CD4 testing) to monitor virologic failure after ART initiation(18-21). In 2018, the President's Emergency Plan for AIDS Relief (PEPFAR) reduced their support for CD4 testing to prioritize viral load monitoring(20). IeDEA has previously shown a decline in pre-ART CD4 testing after adoption of Treat All policies that is steeper in low- and middle-income countries than in high-income countries(18). Trends in median and interquartile range of CD4 count at presentation for care and at ART initiation were stratified by age at presentation for care (< and ≥50 years) to the calendar year through which complete data were available in each region.

Adults presenting for HIV care who had a CD4 count <350 cells/μL at presentation for care were considered "late presenters." The proportion of late presenters was estimated within each age category (<50, 50-64, and 65+ years) for those presenting for care in the most recent complete calendar year of data available.

The most recent, complete calendar years of data contributed by each IeDEA region were as follows: North America: 2018; Central and South America and the Caribbean: 2019; Central Africa: 2019; East Africa: 2019; West Africa: 2017; Southern Africa: 2017; Asia-Pacific: 2019 (Australia sub-cohort: 2016).

Age in IeDEA Regions

The proportion of adults in HIV care who are ≥50-years-old is substantial throughout IeDEA regions ranging from a low of 17% in Southern Africa to 50% in North America (**Figure 1**). The proportions of women and men in care who are ≥50-

years-old are similar in North America and the Central and South America and Caribbean regions; however, there is a lower proportion of older women in care (compared to men) in the African an Asia-Pacific (including the Australian sub-cohort) regions .

A concerning proportion of adults were ≥50-years-old at initial presentation for care: 24% in the North America region; 11% in Central and South America and the Caribbean; 13% in Central Africa; 12% in East Africa; 19% in West Africa;16% in Asia (excluding Australia). The proportion of older adults (≥50-years) initiating ART in Southern Africa was 8% in the Treat All era (**Figure 1 and Table 2**). Differences in the proportion presenting for care at older ages (≥50-years-old) in women vs. men also varied by region: 32% vs. 22% in the North America region; 16% vs. 10% in Central and South America and the Caribbean; 12% vs. 15% in Central Africa; 10% vs. 15% in East Africa; 17% vs. 26% in West Africa; 15% vs. 16% in Asia (excluding Australia); and 7% vs. 9% at ART initiation in the Treat All era in Southern Africa.

While the differences vary by IeDEA region, in nearly every region, PWH ≥50-years-old are presenting with lower CD4 cell counts than their younger adult counterparts (**Figure 2**). Even more concerning, in many regions (Central and South America and the Caribbean, Central Africa, East Africa, and Asia-Pacific Region), the gaps are widening over time as the average CD4 cell count at presentation rises faster in younger adults presenting for care.

Finally, recent IeDEA data (**Table 3**) support findings from the structured review of the literature (**Table 1**). Compared to those less than 50 years of age, those ≥50-years-old are substantially more likely to experience late presentation for care. In most regions, the majority of those ≥50-years-old present late to care.

Discussion

Increasingly, older people are presenting for HIV care. Some of these individuals were recently infected, but a disproportionate number of them have experienced a substantial delay in diagnosis. While it is known that CD4 cell counts decline with age among uninfected individuals(22), these disparities in CD4 cell count at presentation are unlikely to be explained by the biology of aging alone. This is especially true since the gap appears to be widening in much of the world as the CD4 count at presentation is increasing at a faster rate among younger adults who are often targeted for test-and-treat strategies. Further, a natural decline in CD4 cell counts and the phenomenon of accentuated aging with HIV (paper 2 in series “Biologic Ageing in PWH) only underscores the need for earlier diagnosis and treatment for older individuals.

We are concerned that a troubling cycle may be developing. The world’s population is experiencing increased life expectancy in general, increasing the absolute number of older individuals(23). With increased life expectancy, older individuals are continuing to enjoy sexual activity(7, 24, 25) with may be both intra and cross generational(6, 7). Many older individuals also continue to use alcohol and other substances(26, 27). Substance use, age-associated erectile dysfunction, and women being beyond child-bearing age all contribute to inconsistent use of condoms(28, 29), increasing opportunities for HIV transmission. This is concerning because we know that older PWH have delayed presentation for HIV treatment compared with younger PWH, prolonging the period in which they may expose others to infection. Delayed presentation also decreases their ability to benefit from early antiretroviral therapy initiation(8, 30). Increased HIV incidence among older

individuals further increases prevalence and the cycle continues. It is time to tailor language and mediums of communication to reach older individuals more effectively with HIV prevention, diagnosis and treatment interventions.

We need to implement interventions specifically targeting older individuals. Many of these interventions require health system if not national government involvement (Paper 3 in series, "How health systems can adapt to an ageing population of PWH"). No single intervention will fix this problem. Each country and health system will need to consider which of these interventions are most cost effective in their setting:

- Expansion of universal HIV screening
- HIV self-testing
- Routine clinical discussion of sexual health and substance use
- Improved recognition and response to HIV indicator conditions
- Use of electronic decision support to prompt and facilitate HIV testing
- Discussion of pros/cons of PrEP among older adults at-risk for HIV

We discuss each of these in turn recognizing that their feasibility will need to be determined based upon local resource constraints.

Expansion of universal HIV screening

Universal screening has the advantage that it does not require identification of risk and compliance can be easily assessed. Cost-effectiveness studies, using a QALY threshold of $50,000, suggest that screening is justified in any population with a threshold of ≥0.1% undiagnosed HIV prevalence (31-33). Recent work that considered more effective and durable antiretroviral therapy, adoption of test and

treat strategies, and a $100,000 QALY standard found routine testing to be cost-effective at diagnostic rates ≥0.01% (34). This threshold is met (or surpassed) among those ≥65-years-old in many settings. For example, in South Africa the prevalence of HIV in those 50 and more years (7.1%) easily justifies universal screening(35), yet only 54% of those 50 and more years old reported ever testing for HIV compared to 78% of those 25-49 years of age (35). Further, the cost of HIV screening continues to decrease which could lower the threshold for universal screening in the future. Yet, United States Centers for Disease Control and Prevention guidelines for one-time universal screening remain restricted to those between 13 and 64 years(37).

It is time to remove age restrictions on universal screening. When screening *regardless of age* was implemented in the United States Veterans Health Administration in 2009, new HIV diagnoses were established in 0.14% of 210,957 tested from 2009-12 compared to 0.46% of 89,652 tested from 2006-9 under risk based testing(38). Overall, those ≥65-years-old did not cross the threshold (65-74 years: 0.07% (95% CI 0.02 – 0.09%) and those ≥75 years: 0.02% (95% CI 0.01 – 0.03%))(38). However, corresponding with societal inequities, some populations are at greater risk than others; there are circumstances where universal screening of those ≥65-years-old is justified. The investigators found that rates of new diagnoses among Black patients aged 65-74 and ≥75 years were 0.16% (95% CI 0.07-0.24%) and 0.09% (0.00-0.19%), respectively. Ten years ago, based on a 0.1% diagnostic threshold, universal screening would have been justified among Black veterans in care and came close to being justified among all veterans in care aged 65-74 years(38, 39). What we would see now if the study was repeated is not known. It is time to find out.

There are special reasons to shift away from risk-based testing for older individuals. By making HIV testing the default, it would be less stigmatizing(36). In many countries, older individuals are not viewed by health care providers, nor do they see themselves, as “at risk”. They may also be concerned that their privacy will not be protected making them less likely to request testing or to present where testing is provided(36). Further, while all sexual minorities face challenges in having frank discussions of risk behavior with their providers, older sexual minorities face the combined stigma of age and sexual minority status(40). Finally, prior studies have convincingly demonstrated the value of “normalizing” HIV testing(41) possibly by including HIV testing as part of an array of tests for common age-associated illnesses.

HIV Self Testing

Nearly 40% of new HIV infections are transmitted by people who don’t know that they are infected in the United States and proportions may be higher in countries where testing is less accessible(37). However, stigma, fear of isolation from friends and family, and poor HIV health literacy is particularly strong among older people with HIV(36) (Paper 4 “Aging as a PWH” in the series). Further, older individuals are more likely to have established linkages to care for other chronic conditions (Paper 3 How health systems might adapt to an ageing population of PWH). While these pre-existing conditions may make it more likely that physicians will misattribute signs of HIV infection it may also mean that linkage to care is less challenging for older individuals.

Making self-testing more readily available might be particularly helpful for older individuals by empowering them to first learn their diagnosis and then choose

where to seek care(42). This is particularly true for older individuals who are concerned about privacy and/or are sexual minorities(36, 43). Research has begun to identify ideal characteristics of HIV self-tests(44) and, in Agincourt South Africa, home testing is already available (36). Similarly, expanding point-of-care accessibility for testing in resource constrained settings makes sense, so long as a clear linkage to care is possible(45).

Routine clinical discussion of sexual health and substance use

Guidelines recommend annual testing for anyone with active risk behaviors (37), but providers are often unaware of ongoing substance use or risky sex among their older patients and rarely ask (46, 47). They are particularly uncomfortable discussing risky sexual behaviors with older people who are sexual minorities(40). One study characterized primary care physician's response to HIV testing among older patients as, "unnecessary and laughable." Quoting one provider as saying, "older patients are mostly monogamous, so they are low risk, hence low priority…"(48).

Yet older individuals continue to be sexually active, some with multiple intra and cross generational partners(7) and many continue to use alcohol and other substances with multiple implications for their health and well-being including their risk of HIV infection(24, 27, 49). As lifespan has extended, so has sexual healthspan and ongoing sexual activity into older age(49, 50). In South Africa this is particularly true for men who report continuing to have sex with their wives and with younger unmarried women(7). Further, the cohort of individuals currently aging in upper- and middle-income countries commonly used alcohol and other substances in

earlier decades of life and many continue to use these substances as they age, especially alcohol, tobacco, marijuana, and cocaine(27). Injection drug use also occurs but is less common than non-injection use among older individuals.

Providers may feel inhibited about discussing sex with their older patients, but HIV risk is only one of many reasons why providers should ask older patients about their sexual health(24, 25, 49, 50). Older men and women experience challenges to continuing sexual activity including erectile dysfunction for men and vaginal dryness for women, both of which are addressable problems. Erectile dysfunction may make use of a condom very difficult if not impossible(28, 29). Further, most welcome discussion of their sexuality with their providers but prefer that the provider raise the issue(24, 49, 50). This provides a nonthreatening and non-stigmatizing means of asking about sexual risk behaviors and HIV status of their partners as well.

Similarly, there are compelling reasons why providers should also ask older patients about alcohol(26) and other substance use. Unhealthy alcohol use is increasingly common among older individuals(27) and has critically important health implications including risk of cancer(51), liver disease(26), metabolic disease(52), interaction with prescription medications(53), risk of falls and fractures(54), and cognitive decline(55). Non-injection drug use including alcohol use increases disinhibition and leads to risky behaviors including sex with multiple partners and unprotected intercourse(56, 57). When disinhibition is combined with erectile dysfunction and a perceived lack of concern regarding pregnancy, condoms are rarely employed. Individuals in New York City using heroin or cocaine were equally likely to test positive for HIV infection whether their use was via injection or other means(58). Along with multiple sexual partners and injection drug use, non-

injection drug use, including unhealthy alcohol use, should be considered a risk for HIV infection.

Improved recognition and response to HIV indicator conditions

One approach to earlier detection and treatment of HIV infection has been the use of indicator conditions(59-62). The underlying premise is that certain conditions should be considered indications for HIV testing, regardless of disclosed risk behaviors. These conditions fall into three general categories: indicators of risk behaviors that may be undisclosed, indications of early symptomatic HIV disease, and possible indicators of advanced HIV disease. Identified indicators of undisclosed risk behaviors include viral hepatitis and any sexually transmitted infections. Indicators of possible early symptomatic HIV disease include persistent flu like symptoms, a single episode of bacterial pneumonia, herpes zoster, lymphocytopenia, thrombocytopenia and cervical or vulvar dysplasia (CIN2+ or VIN2+). Indicators of possibly advanced HIV disease include cervical cancer, unexplained neuropathy, weight loss, or dementia—while these should always trigger HIV testing, they often occur ten years after initial infection. Tuberculosis also indicates advanced disease but may occur much earlier.

Unfortunately, indicator conditions that might trigger HIV testing among younger individuals may be attributed to other causes in older individuals. Ten years ago, we conducted a study using the US national Veterans Administration data demonstrating that veterans already in care prior to their HIV diagnosis were no more likely to be diagnosed early in the course of their disease as those newly entering VA care(63). Further, only a minority of these patients had an indicator condition prior to their diagnosis. Recently there has been renewed interest in the

use of triggers and these studies have confirmed and extended our findings. These studies underscore that trigger conditions are more common among older individuals, but less commonly prompt HIV testing in this age group(59-62).

Use of electronic decision support to prompt and facilitate HIV testing

There is a practical problem with all the HIV testing strategies we have discussed. All these strategies require individuals who are not focused on HIV or its treatment to consider the possibility of HIV infection, obtain the test, and act on the results.

For many primary care and specialty providers in higher-income countries throughout North America, Europe, and Australia/New Zealand, few things are further from their clinical focus. Even in countries with higher HIV prevalence and greater general awareness, providers may not consider testing older individuals who they deem to be at lower risk. In this context, 20 years of experience with a fully paperless, national, electronic medical record in the US Veterans Healthcare System may offer important insights(48, 64-67). Electronic health record (EHR) clinical reminders may help overcome documented failures of one-time universal screening, and risk based and indicator condition testing.

When effectively implemented and maintained, universal screening facilitates more timely diagnoses of HIV infection. In August 2009, The US Veterans Health Administration (VA) revised its HIV testing policies to promote voluntary routine one-time testing of all adults regardless of age and to streamline testing procedures through a clinical reminder. Streamlining eventually included a transition from requiring written informed consent to verbal consent. These changes tripled the lifetime HIV testing prevalence within the national VA(38).

A multimodal HIV testing intervention was also launched with site-specific study teams consisting of an infectious disease specialist, a primary care team leader, and other stakeholders. The intervention included an electronic clinical reminder, a multifaceted provider activation program, social marketing to providers and patients, regular informal conversations with providers, and quarterly feedback on rates of testing.(48) The proportion of newly diagnosed persons ≥60-years-old increased from 7.5% to 15.3% (p=0.10) and the proportion of patients with CD4 cell counts <200 cells/μL decreased from 43% to 29% (p=0.04). A facility that implemented only the electronic reminder linked to a test order achieved the same improvement in testing as the facility with the full multimodal intervention suggesting that this was the element most critical to success(68). Similarly, clinical prompts could also improve adherence to risk based and indicator condition testing.

For resource limited settings, innovative approaches using solar power(69), cloud based systems(70), and mobile phone applications(71) for data entry have been developed to support EHRs in the context of intermittent, or non-existent, electricity. These have been successfully applied in Kenya(72), India(73), and other low to middle-income countries(74). They have already demonstrated effectiveness at improving the timing of antiretroviral treatment in Kenya(70).

Discussion of pros/cons of PrEP among older adults at risk for HIV

Among those at substantial risk of HIV infection, a frank discussion of the pros/cons of pre-exposure prophylaxis (PrEP), tailored to this age group, is indicated. Importantly, based on studies focused on HIV and non-HIV medications, older individuals are more capable of achieving excellent medication adherence than younger individuals(75). On the other hand, addition of two antiretrovirals (a

fixed dose, single-tablet combination of tenofovir (300 mg) and emtricitabine (200 mg)) to a medication regimen that may already cross the line into polypharmacy (≥5 chronic medications) (76) and increased risks of hospitalization and mortality(76) has its downside. Polypharmacy is a growing problem among older individuals(77) and the long term safety of these medications in individuals 65 years of age or older is largely unknown(78).

Tenofovir is associated with nephrotoxicity and is contraindicated for those with a creatinine clearance less than 60 mL/min(79, 80). Tenofovir is also associated with bone loss and may contribute to osteoporosis (79, 80), a particular concern among older individuals, especially women. A careful consideration of what other medications the individual is taking and whether these toxicities might exacerbate those of the other medications is indicated(78).

Further, before initiating PrEP, patients must be tested for HIV since PrEP is not an effective treatment for HIV infection and can lead to viral resistance. While receiving PrEP, patients should be monitored every 3 months for declining renal function, sexually transmitted infections, and HIV infection. All this may seem like too much additional effort to patients who may only have sexual intercourse or use injection drugs intermittently(81).

Momentum is building for “on-demand” PrEP(80, 82, 83). The IPERGAY (Intervention Preventive de l’Exposition aux Risques avec et pour les Gays) randomized MSM to receive pericoital PrEP—two pills between 2 and 24 hours before anal intercourse and one pill daily for two days following sex but not more than 7 pills in a single week. This might substantially curtail concerns about toxicity. While this may be an appealing solution, further work is clearly needed.

Conclusion

Although older individuals more commonly present for HIV care late and have more contact with the healthcare system, few studies have focused on factors associated with late presentation specifically among older individuals. This is important because older age is independently associated with risk for indicator conditions possibly rendering them less informative for detection of undiagnosed HIV infection. As the population of older adults with HIV continues to grow, in-depth studies are needed to inform guidelines for HIV testing and determine how best to implement more wide-spread testing and earlier diagnosis and treatment in this growing age group.

1. Tavoschi L, Gomes Dias J, Pharris A. New HIV diagnoses among adults aged 50 years or older in 31 European countries, 2004-15: an analysis of surveillance data. The lancet HIV. 2017;4(11):e514-e21.
2. Autenrieth CS, Beck EJ, Stelzle D, Mallouris C, Mahy M, Ghys P. Global and regional trends of people living with HIV aged 50 and over: Estimates and projections for 2000-2020. PLoS One. 2018;13(11):e0207005.
3. Puhr R, Kumarasamy N, Ly PS, Ng OT, Van Nguyen K, Merati TP, et al. HIV and Aging: Demographic Change in the Asia-Pacific Region. J Acquir Immune Defic Syndr. 2017;74(5):e146-e8.
4. Caro-Vega Y, Belaunzarán-Zamudio PF, Crabtree-Ramírez B, Shepherd BE, Mejia F, Giganti MJ, et al. Trends in proportion of older HIV-infected people in care in Latin America and the Caribbean: a growing challenge. Epidemiol Infect. 2018;146(10):1308-11.
5. Prevention CfDCa. Estimated HIV incidence and prevalence in the United States, 2015-2019. Atlanta, Georgia: Cetners for Disease Control and Prevention; 2021.
6. Gómez-Olivé FX, Houle B, Rosenberg M, Kabudula C, Mojola S, Rohr JK, et al. Brief Report: HIV Incidence Among Older Adults in a Rural South African Setting: 2010-2015. J Acquir Immune Defic Syndr. 2020;85(1):18-22.
7. Houle B, Mojola SA, Angotti N, Schatz E, Gómez-Olivé FX, Clark SJ, et al. Sexual behavior and HIV risk across the life course in rural South Africa: trends and comparisons. AIDS Care. 2018;30(11):1435-43.
8. Cornell M, Johnson LF, Schomaker M, Tanser F, Maskew M, Wood R, et al. Age in antiretroviral therapy programmes in South Africa: a retrospective, multicentre, observational cohort study. The lancet HIV. 2015;2(9):e368-75.
9. Althoff KN, Gebo KA, Gange SJ, Klein MB, Brooks JT, Hogg RS, et al. CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation? AIDS Res Ther. 2010;7:45.
10. Gesesew HA, Ward P, Woldemichael K, Mwanri L. Late presentation for HIV care in Southwest Ethiopia in 2003-2015: prevalence, trend, outcomes and risk factors. BMC infectious diseases. 2018;18(1):59.
11. Taborelli M, Virdone S, Camoni L, Regine V, Zucchetto A, Frova L, et al. The persistent problem of late HIV diagnosis in people with AIDS: a population-based study in Italy, 1999-2013. Public Health. 2017;142:39-45.
12. Nduaguba SO, Ford KH, Wilson JP, Lawson KA, Cook RL. Identifying subgroups within at-risk populations that drive late HIV diagnosis in a Southern U.S. state. Int J STD AIDS. 2021;32(2):162-9.
13. Meléndez J, Reinhardt SW, O'Halloran JA, Spec A, Alonzo Cordon A, Powderly WG, et al. Late Presentation and Missed Opportunities for HIV Diagnosis in Guatemala. AIDS and behavior. 2019;23(4):920-8.
14. O'Connell S, Enkelmann J, Sadlier C, Bergin C. Late HIV presentation - missed opportunities and factors associated with a changing pattern over time. Int J STD AIDS. 2017;28(8):814-21.
15. Levy I, Maor Y, Mahroum N, Olmer L, Wieder A, Litchevski V, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. BMJ open. 2016;6(11):e012721.
16. Gullón A, Verdejo J, de Miguel R, Gómez A, Sanz J. Factors associated with late diagnosis of HIV infection and missed opportunities for earlier testing. AIDS Care. 2016;28(10):1296-300.

17. Lin YD, Garner SE, Lau JSY, Korman TM, Woolley IJ. Prevalence of HIV indicator conditions in late presenting patients with HIV: a missed opportunity for diagnosis? Qjm. 2019;112(1):17-21.
18. Brazier E, Tymejczyk O, Zaniewski E, Egger M, Wools-Kaloustian K, Yiannoutsos CT, et al. Effects of national adoption of Treat-All guidelines on pre-ART CD4 testing and viral load monitoring after ART initiation: A regression discontinuity analysis. Clin Infect Dis. 2021.
19. Nash D, Robertson M. How to Evolve the Response to the Global HIV Epidemic With New Metrics and Targets Based on Pre-Treatment CD4 Counts. Curr HIV/AIDS Rep. 2019;16(4):304-13.
20. Foundation HJKF. The U.S. Government Engagement in Global Health: a Primer. 2019.
21. Organization. WH. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendations for a Public Health Approach. Geneva, Switzerland: World Health Organization; 2013.
22. Maini MK, Gilson RJ, Chavda N, Gill S, Fakoya A, Ross EJ, et al. Reference ranges and sources of variability of CD4 counts in HIV-seronegative women and men. GenitourinMed. 1996;72(1):27-31.
23. United Nations doEaSA, Population Division(2019). World Population Ageing 2019: Highlights. New York: United Nations; 2019.
24. Lindau ST, Gavrilova N. Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. Bmj. 2010;340:c810.
25. Nicolosi A, Buvat J, Glasser DB, Hartmann U, Laumann EO, Gingell C. Sexual behaviour, sexual dysfunctions and related help seeking patterns in middle-aged and elderly Europeans: the global study of sexual attitudes and behaviors. World J Urol. 2006;24(4):423-8.
26. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018.
27. Kuerbis A. Substance Use among Older Adults: An Update on Prevalence, Etiology, Assessment, and Intervention. Gerontology. 2020;66(3):249-58.
28. Ehrenstein V, Horton NJ, Samet JH. Inconsistent condom use among HIV-infected patients with alcohol problems. Drug Alcohol Depend. 2004;73(2):159-66.
29. Schick V, Herbenick D, Reece M, Sanders SA, Dodge B, Middlestadt SE, et al. Sexual behaviors, condom use, and sexual health of Americans over 50: implications for sexual health promotion for older adults. The journal of sexual medicine. 2010;7 Suppl 5:315-29.
30. Shamu T, Chimbetete C, Egger M, Mudzviti T. Treatment outcomes in HIV infected patients older than 50 years attending an HIV clinic in Harare, Zimbabwe: A cohort study. PLOS ONE. 2021;16(6):e0253000.
31. Bert F, Gualano MR, Biancone P, Brescia V, Camussi E, Martorana M, et al. Cost-effectiveness of HIV screening in high-income countries: A systematic review. Health Policy. 2018;122(5):533-47.
32. Paltiel AD, Weinstein MC, Kimmel AD, Seage GR, III, Losina E, Zhang H, et al. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. NEnglJMed. 2005;352(6):586-95.
33. Sanders GD, Bayoumi AM, Holodniy M, Owens DK. Cost-effectiveness of HIV screening in patients older than 55 years of age. Ann Intern Med. 2008;148(12):889-903.

34. Lucas A, Armbruster B. The cost-effectiveness of expanded HIV screening in the United States. AIDS. 2013;27(5):795-801.
35. Schatz E, Knight L. "I was referred from the other side": Gender and HIV testing among older South Africans living with HIV. PLoS One. 2018;13(4):e0196158.
36. Schatz E, Houle B, Mojola SA, Angotti N, Williams J. How to "Live a Good Life": Aging and HIV Testing in Rural South Africa. J Aging Health. 2019;31(4):709-32.
37. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006;55(Rr-14):1-17; quiz CE1-4.
38. Goetz MB, Hoang T, Kan VL, Rimland D, Rodriguez-Barradas MC, Asch SM. Rates and Predictors of Newly Diagnosed HIV Infection Among Veterans Receiving Routine Once-Per-Lifetime HIV Testing in the Veterans Health Administration. J Acquir Immune Defic Syndr. 2015;69(5):544-50.
39. Owens DK, Sundaram V, Lazzeroni LC, Douglass LR, Sanders GD, Taylor K, et al. Prevalence of HIV infection among inpatients and outpatients in Department of Veterans Affairs health care systems: implications for screening programs for HIV. Am J Public Health. 2007;97(12):2173-8.
40. Flatt JD, Cicero EC, Kittle KR, Brennan-Ing M. Recommendations for Advancing Research with Sexual and Gender Minority Older Adults. J Gerontol B Psychol Sci Soc Sci. 2021.
41. Bokhour BG, Solomon JL, Knapp H, Asch SM, Gifford AL. Barriers and facilitators to routine HIV testing in VA primary care. J Gen Intern Med. 2009;24(10):1109-14.
42. Orne-Gliemann J, Zuma T, Chikovore J, Gillespie N, Grant M, Iwuji C, et al. Community perceptions of repeat HIV-testing: experiences of the ANRS 12249 Treatment as Prevention trial in rural South Africa. AIDS Care. 2016;28 Suppl 3:14-23.
43. Johnson MC, Chung R, Leung SJ, Edelstein Z, Yuan Y, Flavin SM. Combating Stigma Through HIV Self-Testing: New York State's HIV Home Test Giveaway Program for Sexual Minorities. J Public Health Manag Pract. 2020.
44. Knight L, Makusha T, Lim J, Peck R, Taegtmeyer M, van Rooyen H. "I think it is right": a qualitative exploration of the acceptability and desired future use of oral swab and finger-prick HIV self-tests by lay users in KwaZulu-Natal, South Africa. BMC research notes. 2017;10(1):486.
45. Manoto SL, Lugongolo M, Govender U, Mthunzi-Kufa P. Point of Care Diagnostics for HIV in Resource Limited Settings: An Overview. Medicina (Kaunas). 2018;54(1).
46. Dookeran NM, Burgess JF, Jr., Bowman CC, Goetz MB, Asch SM, Gifford AL. HIV screening among substance-abusing veterans in care. Journal of substance abuse treatment. 2009;37(3):286-91.
47. Inelmen EM, Sergi G, De Rui M, Manzato E. Enhancing awareness to mitigate the risk of HIV/AIDS in older adults. Aging Clin Exp Res. 2014;26(6):665-9.
48. Bokhour BG, Saifu H, Goetz MB, Fix GM, Burgess J, Fletcher MD, et al. The role of evidence and context for implementing a multimodal intervention to increase HIV testing. Implement Sci. 2015;10:22.
49. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762-74.

50. Ni Lochlainn M, Kenny RA. Sexual activity and aging. J Am Med Dir Assoc. 2013;14(8):565-72.
51. Rumgay H SK, Charvat H, et al. . Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. Lancet Oncol. 2021.
52. Fan AZ, Russell M, Naimi T, Li Y, Liao Y, Jiles R, et al. Patterns of alcohol consumption and the metabolic syndrome. JClinEndocrinolMetab. 2008;93(10):3833-8.
53. Lindsey WT, Stewart D, Childress D. Drug interactions between common illicit drugs and prescription therapies. Am J Drug Alcohol Abuse. 2012;38(4):334-43.
54. Womack JA, Murphy TE, Rentsch CT, Tate JP, Bathulapalli H, Smith AC, et al. Polypharmacy, hazardous alcohol and illicit substance use and serious falls among PLWH and uninfected comparators. J Acquir Immune Defic Syndr. 2019.
55. Krivanek TJ, Gale SA, McFeeley BM, Nicastri CM, Daffner KR. Promoting Successful Cognitive Aging: A Ten-Year Update. J Alzheimers Dis. 2021;81(3):871-920.
56. Cook RL, McGinnis KA, Kraemer KL, Gordon AJ, Conigliaro J, Maisto SA, et al. Intoxication before intercourse and risky sexual behavior in male veterans with and without human immunodeficiency virus infection. Med Care. 2006;44(8 Suppl 2):S31-S6.
57. Cook RL, McGinnis KA, Samet JH, Fiellin DA, Rodriquez-Barradas MC, Kraemer KL, et al. Erectile dysfunction drug receipt, risky sexual behavior and sexually transmitted diseases in HIV-infected and HIV-uninfected men. J Gen Intern Med. 2010;25(2):115-21.
58. Des Jarlais DC, Arasteh K, Perlis T, Hagan H, Abdul-Quader A, Heckathorn DD, et al. Convergence of HIV seroprevalence among injecting and non-injecting drug users in New York City. Aids. 2007;21(2):231-5.
59. Basoulis D, Kostaki EG, Paraskevis D, Hatzakis A, Psichogiou M. Tracking missed opportunities for an early HIV diagnosis in a population of people living with HIV with known time of infection. Sexually transmitted infections. 2021.
60. Raben D, Sullivan AK, Mocroft A, Kutsyna G, Hadžiosmanović V, Vassilenko A, et al. Improving the evidence for indicator condition guided HIV testing in Europe: Results from the HIDES II Study - 2012 - 2015. PLoS One. 2019;14(8):e0220108.
61. Lhopitallier L, Moulin E, Hugli O, Cavassini M, Darling KEA. Missed opportunities for HIV testing among patients newly presenting for HIV care at a Swiss university hospital: a retrospective analysis. BMJ open. 2018;8(6):e019806.
62. Bogers SJ, Hulstein SH, Schim van der Loeff MF, de Bree GJ, Reiss P, van Bergen J, et al. Current evidence on the adoption of indicator condition guided testing for HIV in western countries: A systematic review and meta-analysis. EClinicalMedicine. 2021;35:100877.
63. Gandhi NR, Skanderson M, Gordon KS, Concato J, Justice AC. Delayed presentation for human immunodeficiency virus (HIV) care among veterans: a problem of access or screening? Med Care. 2007;45(11):1105-9.
64. Goetz MB, Hoang T, Knapp H, Burgess J, Fletcher MD, Gifford AL, et al. Central implementation strategies outperform local ones in improving HIV testing in Veterans Healthcare Administration facilities. J Gen Intern Med. 2013;28(10):1311-7.
65. Gidwani R, Goetz MB, Kominski G, Asch S, Mattocks K, Samet JH, et al. A budget impact analysis of rapid human immunodeficiency virus screening in Veterans Administration emergency departments. J Emerg Med. 2012;42(6):719-26.

66. Goetz MB, Hoang T, Knapp H, Henry SR, Anaya H, Chou AF, et al. Exportability of an intervention to increase HIV testing in the Veterans Health Administration. Jt Comm J Qual Patient Saf. 2011;37(12):553-9.
67. Goetz MB, Hoang T, Henry SR, Knapp H, Anaya HD, Gifford AL, et al. Evaluation of the sustainability of an intervention to increase HIV testing. J Gen Intern Med. 2009;24(12):1275-80.
68. Goetz MB, Rimland D. Effect of expanded HIV testing programs on the status of newly diagnosed HIV-infected patients in two Veterans Health Administration facilities: 1999-2009. J Acquir Immune Defic Syndr. 2011;57(2):e23-5.
69. Tierney WM, Rotich JK, Smith FE, Bii J, Einterz RM, Hannan TJ. Crossing the "digital divide" implementing an electronic medical record system in a rural Kenyan health center to support clinical care and research. Proc AMIA Symp. 2002;:792-5.:792-5.
70. Haskew J, Rø G, Turner K, Kimanga D, Sirengo M, Sharif S. Implementation of a Cloud-Based Electronic Medical Record to Reduce Gaps in the HIV Treatment Continuum in Rural Kenya. PLoS One. 2015;10(8):e0135361.
71. Rotich JK, Hannan TJ, Smith FE, Bii J, Odero WW, Vu N, et al. Installing and implementing a computer-based patient record system in sub-Saharan Africa: the Mosoriot Medical Record System. JAmMedInformAssoc. 2003;10(4):295-303.
72. Oyugi B, Makunja S, Kabuti W, Nyongesa C, Schömburg M, Kibe V, et al. Improving the management of hypertension and diabetes: An implementation evaluation of an electronic medical record system in Nairobi County, Kenya. Int J Med Inform. 2020;141:104220.
73. Patel SA, Sharma H, Mohan S, Weber MB, Jindal D, Jarhyan P, et al. The Integrated Tracking, Referral, and Electronic Decision Support, and Care Coordination (I-TREC) program: scalable strategies for the management of hypertension and diabetes within the government healthcare system of India. BMC Health Serv Res. 2020;20(1):1022.
74. Dainton C, Chu CH. A review of electronic medical record keeping on mobile medical service trips in austere settings. Int J Med Inform. 2017;98:33-40.
75. C.I. G, B.M. G. Drug therapy of the aged: The problem of compliance and the roles of physicians and pharmacists. J AmGeriatr Soc. 1984;32:301-7.
76. Edelman EJ, Rentsch CT, Justice AC. Polypharmacy in HIV: recent insights and future directions. Curr Opin HIV AIDS. 2020;15(2):126-33.
77. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opin Drug Saf. 2018;17(12):1185-96.
78. Franconi I, Guaraldi G. Pre-exposure Prophylaxis for HIV Infection in the Older Patient: What can be Recommended? Drugs Aging. 2018;35(6):485-91.
79. Liegeon G, Antoni G, Pialoux G, Capitant C, Cotte L, Charreau I, et al. Changes in kidney function among men having sex with men starting on demand tenofovir disoproxil fumarate - emtricitabine for HIV pre-exposure prophylaxis. Journal of the International AIDS Society. 2020;23(2):e25420.
80. Saberi P, Scott HM. On-Demand Oral Pre-exposure Prophylaxis with Tenofovir/Emtricitabine: What Every Clinician Needs to Know. J Gen Intern Med. 2020;35(4):1285-8.
81. Beymer MR, Holloway IW, Pulsipher C, Landovitz RJ. Current and Future PrEP Medications and Modalities: On-demand, Injectables, and Topicals. Curr HIV/AIDS Rep. 2019;16(4):349-58.

82. Rutstein SE, Smith DK, Dalal S, Baggaley RC, Cohen MS. Initiation, discontinuation, and restarting HIV pre-exposure prophylaxis: ongoing implementation strategies. The lancet HIV. 2020;7(10):e721-e30.
83. Siguier M, Mera R, Pialoux G, Ohayon M, Cotte L, Valin N, et al. First year of pre-exposure prophylaxis implementation in France with daily or on-demand tenofovir disoproxil fumarate/emtricitabine. The Journal of antimicrobial chemotherapy. 2019;74(9):2752-8.

Search strategy and selection criteria

References for this Review were identified through a search of PubMed on 5/19/2021 using the search terms (“late presentation” or “delayed diagnosis”) and “HIV” restricted to manuscripts published at least in part in English in the last 5 years. This yielded 371 citations. We required that the manuscript be original research, include an adult population (age>15 years), define late presentation, and adequately characterize the sample evaluated including sample size, region and calendar period from which the sample was drawn, and the proportion or number of late presenters. A review of titles and abstracts eliminated all but 74 manuscripts. When these were further restricted to manuscripts reporting the association of age with late presentation the number reduced to 40.

Declaration of Interests

ACJ has no conflict of interest.

Authors’ Contributions

Table 1. Structured Review of Delayed Presentation Publications Last Five Years

1st Author	Definition of Late Presenter	New Diagnoses (n)	Late Presenters (n, %)		Years	Location	Age Variable (Yrs)	Odds Ratio	95% CI	
Gardner	AIDS	1385	422	31%	2009-14	USA (single site)	65+ vs. 25-44	1.3	0.6	2.6
Nduaguba	AIDS	77844	30359	39%	1996-2001	USA (multisite)	60+ vs<30	4.0	3.3	4.7
Nduaguba	AIDS	77844	30359	39%	2002-2007	USA (multisite)	60+ vs<30	4.6	3.9	5.4
Kwobah	CD4<100	10533	2421	23%	2010-11	Kenya (multisite)	>24 vs. <19	1.6	1.0	2.6
Kadam	CD4<200	659	264	40%	2011-15	India (single site)	continuous variable	na		
Honge	CD4<200	3720	1810	48%	2005-13	West Africa (single site)	50+ vs.<30	1.5	1.1	2.0
Senard	CD4<200	186	49	26%	2012-13	France (single site)	continuous variable	1.1	1.0	1.1
Taborelli	CD4<200 or AIDS	16601	7720	47%	1999-13	Italy (multisite) Italians	50+ vs.35-49	1.5	1.4	1.7
Taborelli	CD4<200 or AIDS	4152	2831	68%	1999-14	Italy (multisite) Non- Italians	50+ vs.35-49	0.9	0.7	1.2
Tang	CD4<200 or AIDS	528234	179700	34%	2006-14	China (multisite)	55+ vs.15-24	2.9	2.9	3.0
Mohammadi	CD4<350	4402	2562	58%	1987-2016	Iran (158 sites)	50+ vs.<30	3.6	2.6	4.8
Rava	CD4<350	14876	6635	45%	2004-18	Spain (46 sites)	50+ vs. <30	2.8	2.5	3.1
Ribeiro	CD4<350	356	218	59%	2017	Brazil (single site)	continuous variable	1.0	1.0	1.1
Bath	CD4<350	2469	1342	54%	2008-14	England (multisite)	55+ vs. 16-19	3.5	1.6	7.7
Cuzin	CD4<350	1421	625	44%	2014-15	France (10 sites)	>47 vs. <29	1.9	1.4	2.5
MacCarthy	CD4<350	1970	698	61%	2010	Brazil (3 sites)	45+ vs.18-44	1.7	1.1	2.5
Hu	CD4<350	519	188	38%	2011-14	China (8 cities)	40+ vs.18-24	3.1	1.8	5.5
Gullon	CD4<350	316	158	50%	2007-14	Spain (single site)	>38 vs. <38	2.2	1.3	3.7
Schafer	CD4<350	165	105	64%	2009-11	Germany (single site)	mean age LP 41 vs 32	na		
Miranda	CD4<350 or AIDS	907	459	51%	1984-2017	Portugal (single site)	>56 vs. <30	2.9	1.5	5.9
Jablonowska	CD4<350 or AIDS	1522	682	45%	2016-17	Poland (13 sites)	per decade	1.5	1.4	1.7
Robles	CD4<350 or AIDS	3842	2793	73%	2012-17	Panama (multisite)	>65 vs. 18-24	2.9	1.7	5.0

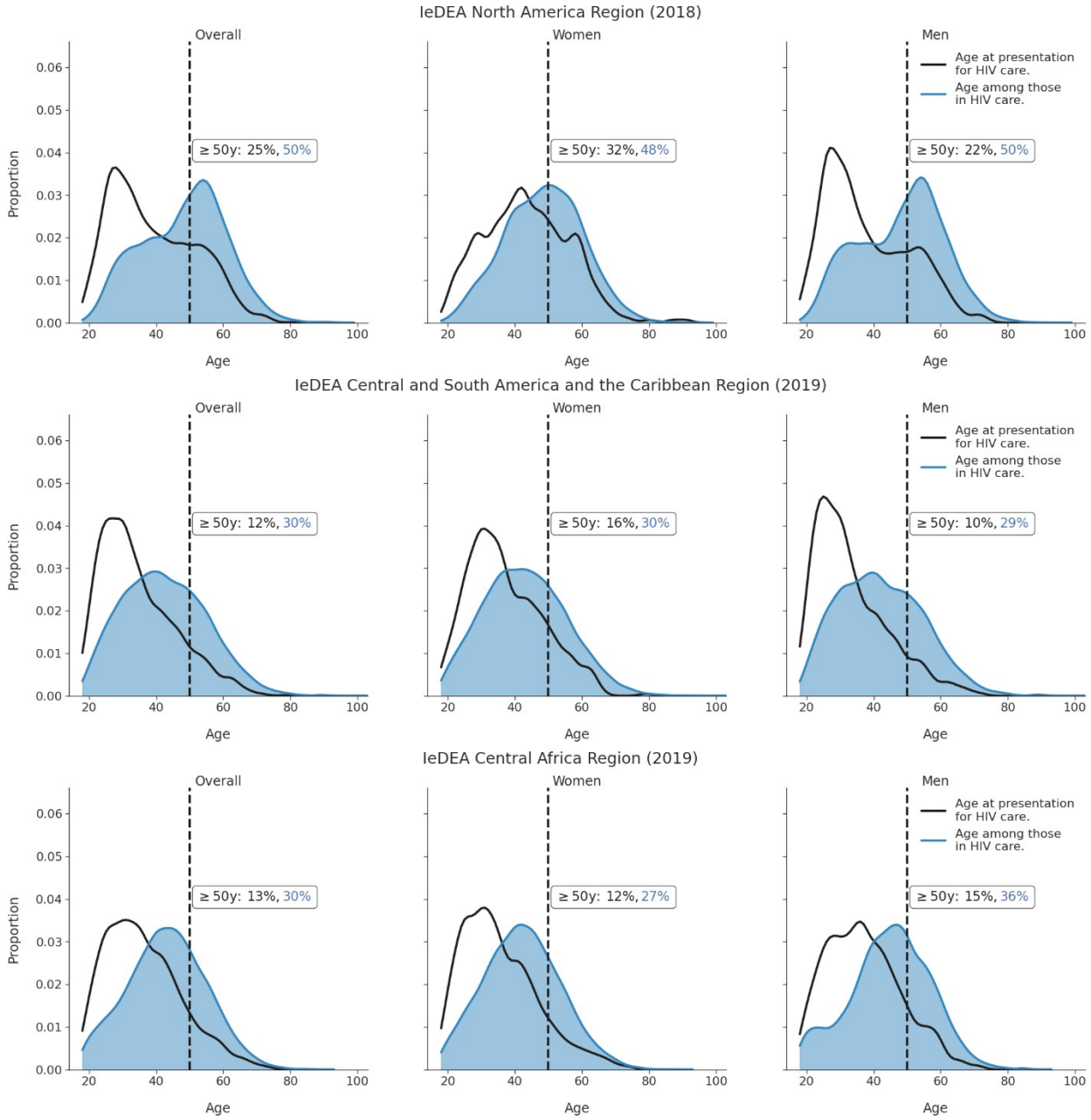
Palacios-Baena	CD4<350 or AIDS	205	102	50 %	2014-18	Spain (single site)	32+ vs. <32	3.4	1.9	6.1
Muelas Fernandez	CD4<350 or AIDS	74	33	45 %	2013-18	Spain (single site)	40+ vs. <40	2.6	1.0	6.9
Karaosmanoglu	CD4<350 or AIDS	1673	826	49 %	2003-16	Turkey (single site)	>50 vs ≤50	1.8	*	*
Krueger	CD4<350 or AIDS	1644585	Na	na	2013-16	USA (multisite)	45+ vs. 25-44	1.7	*	*
Siwak	CD4<350 or AIDS	3972	2288	58 %	2000-15	Poland (14 sites)	60+ vs.≤20	5.2	1.9	14.0
Hu	CD4<350 or AIDS	45118	31673	70 %	2012-16	China (multisite)	>50 vs. 15-30	1.5	1.4	1.6
Zhonghua	CD4<350 or AIDS	293187	200503	68 %	2009-17	China (multisite)	60+ vs. 18-29	2.3	2.3	2.4
Wilton	CD4<350 or AIDS	1819	1476	54 %	1999-2013	Canada (multisite)	50+ vs.<30	2.8	1.9	4.1
Lin	CD4<350 or AIDS	436	82	19 %	2000-14	Australia (single site)	mean age LP 45 vs 39	na		
Rao	CD4<350 or AIDS	474	356	75 %	2012-13	India (single site)	≤50 vs.≤25	4.2	1.3	13.2
Darcis	CD4<350 or AIDS	687	302	44 %	2006-17	Belgium (single site)	10 year increments	1.3	1.1	1.5
Wojcik-Cichy	CD4<350 or AIDS	412	259	63 %	2009-16	Poland (single site)	10 year increments	1.8	1.4	2.4
Johnson	CD4<350 or AIDS	401	307	77 %	2013-16	Sudan (single site)	34+ vs. <34	na		
Jin	CD4<350 or AIDS	7073	2949	42 %	2011-15	China (multisite)	60+ vs. 0-19	2.2	1.5	3.1
Gesesew	CD4<350 or AIDS	4900	3268	67 %	2003-15	Ethiopia (single site)	50+ vs. 15-24	0.4	0.3	0.6
Fomundam	CD4<350 or AIDS	8138	4817	59 %	2014-15	South Africa (35 sites)	50+ vs. <50	1.9	*	*
Levy	CD4<350 or AIDS	356	118	33 %	2010-15	Israel (single site)	>50 vs. <50	2.4	1.1	5.0
Raffetti	CD4<350 or AIDS	19391	10471	54 %	1985-2013	Italy (multisite)	55+ vs.<25	7.5	6.1	9.2
Brannstrom	CD4<350 or AIDS	575	334	58 %	2009-12	Sweden (12 sites)	≥50 vs.≤30	4.0	2.1	7.6
Kesselring	CD4<500	702	442	63 %	2013-15	Canada (multisite)	continuous variable	1.0	1.02	1.05

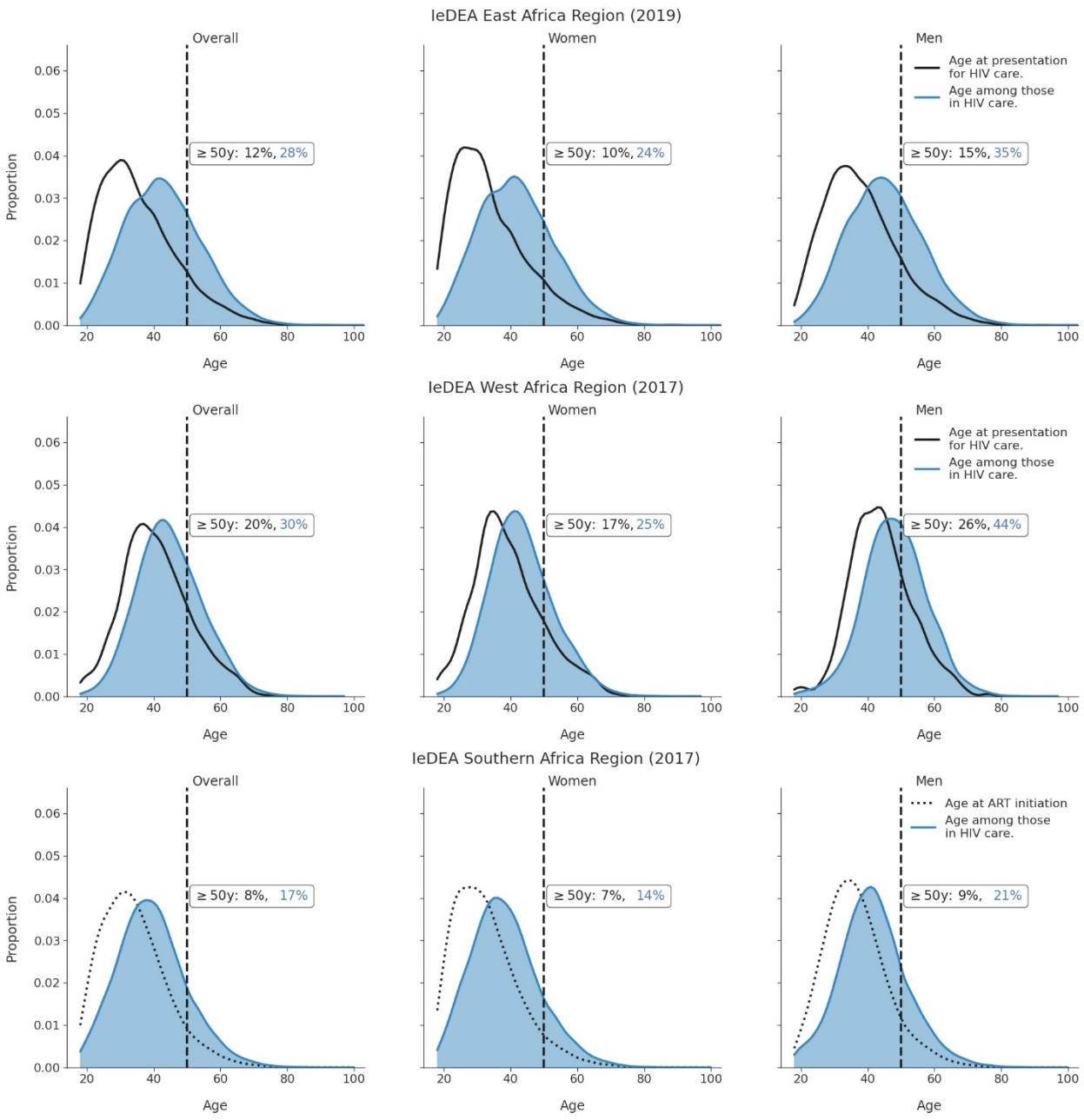
Table 2: Age at presentation for HIV care or ART initiation, IeDEA regions

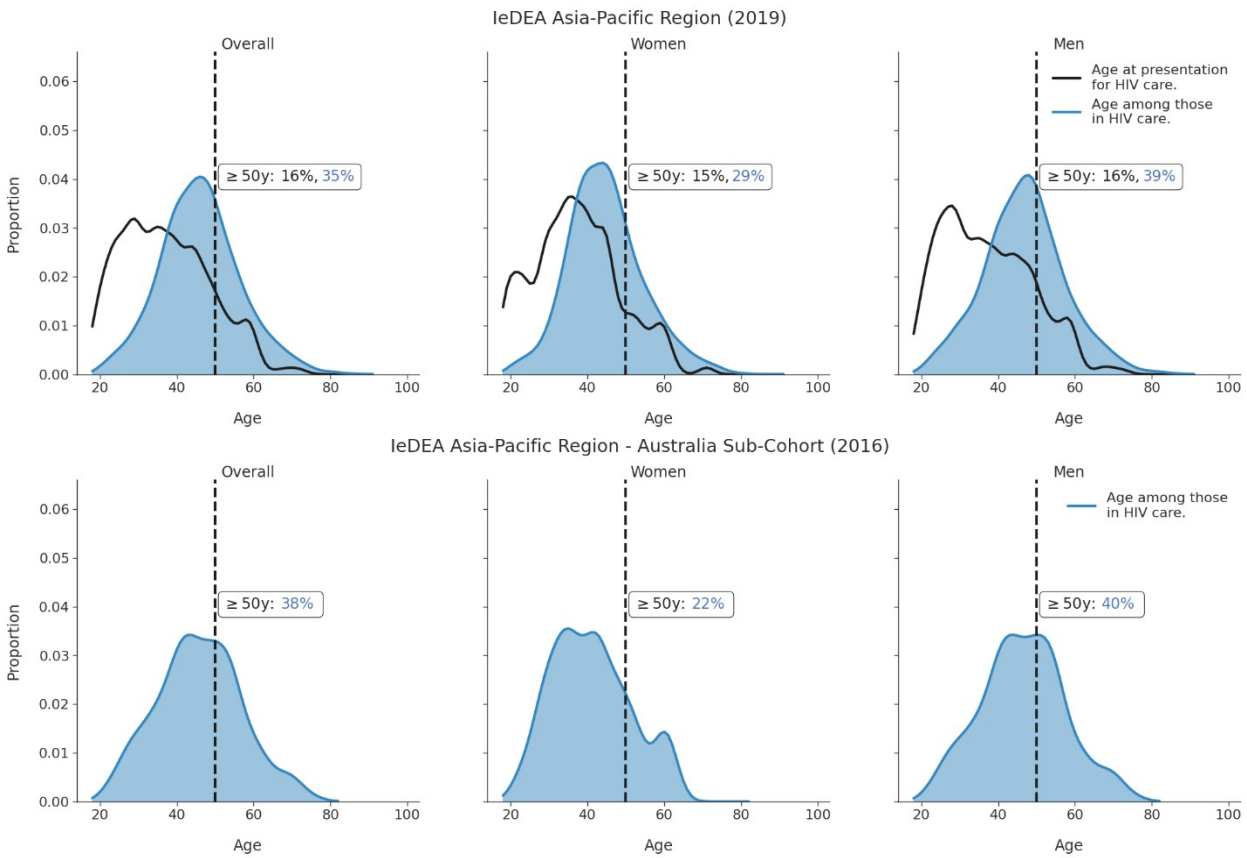
IeDEA Region	N presenting for care or ART initiation	% <50 at presentation or ART initiation	% 50-64 at presentation or ART initiation	% 65+ at presentation or ART initiation
Presenting for care				
North America (2018)	1,000-1,500	76%	21%	3%
Central and South America & the Caribbean (2019)	1,000-1,500	89%	10%	1%
Central Africa (2019)	1,500-2,000	87%	11%	2%
East Africa (2019)	10,000-10,500	88%	10%	2%
West Africa (2017)	1,000-1,500	81%	17%	2%
Asia-Pacific (2019)	500-1,000	84%	14%	1%
Initiating ART (in the Treat All era)				
Southern Africa (2017)	22,000-22,500	93%	7%	1%

Footnotes:
In the IeDEA Southern Africa regional cohort, participants are observed at ART initiation (as opposed to at presentation for HIV care) and then followed forward in time; age at ART initiation is believed to be reflective of age at presentation for HIV care as of 2017 when the “Treat All” guidelines were adopted in Southern Africa. Estimates of age at presentation for HIV care are not presented for the Australia sub-cohort of the IeDEA Asia-Pacific region. Participants were recruited to replenish the Australian sub-cohort in 2016; the median age at presentation for HIV care is based on a relatively small sub-population (<20 participants) of those presenting for HIV care at participating IeDEA clinics. Presenting estimates in these age groups would involve subgroups of <5, which breaches confidentiality arrangements.

Figure 1: Age at presentation for HIV care (black line), and among all of those in HIV care (blue shading), in the most recent complete calendar year of data available, by sex (left: women, right: men), IeDEA regions




IeDEA East Africa Region (2019)
Overall
Women
Men
Age at presentation for HIV care.
Age among those in HIV care.
≥ 50y: 12%, 28%
≥ 50y: 10%, 24%
≥ 50y: 15%, 35%
IeDEA West Africa Region (2017)
Overall
Women
Men
Age at presentation for HIV care.
Age among those in HIV care.
≥ 50y: 20%, 30%
≥ 50y: 17%, 25%
≥ 50y: 26%, 44%
IeDEA Southern Africa Region (2017)
Overall
Women
Men
Age at ART initiation
Age among those in HIV care.
≥ 50y: 8%, 17%
≥ 50y: 7%, 14%
≥ 50y: 9%, 21%
Proportion
Age
0.00
0.01
0.02
0.03
0.04
0.05
0.06
20
40
60
80
100



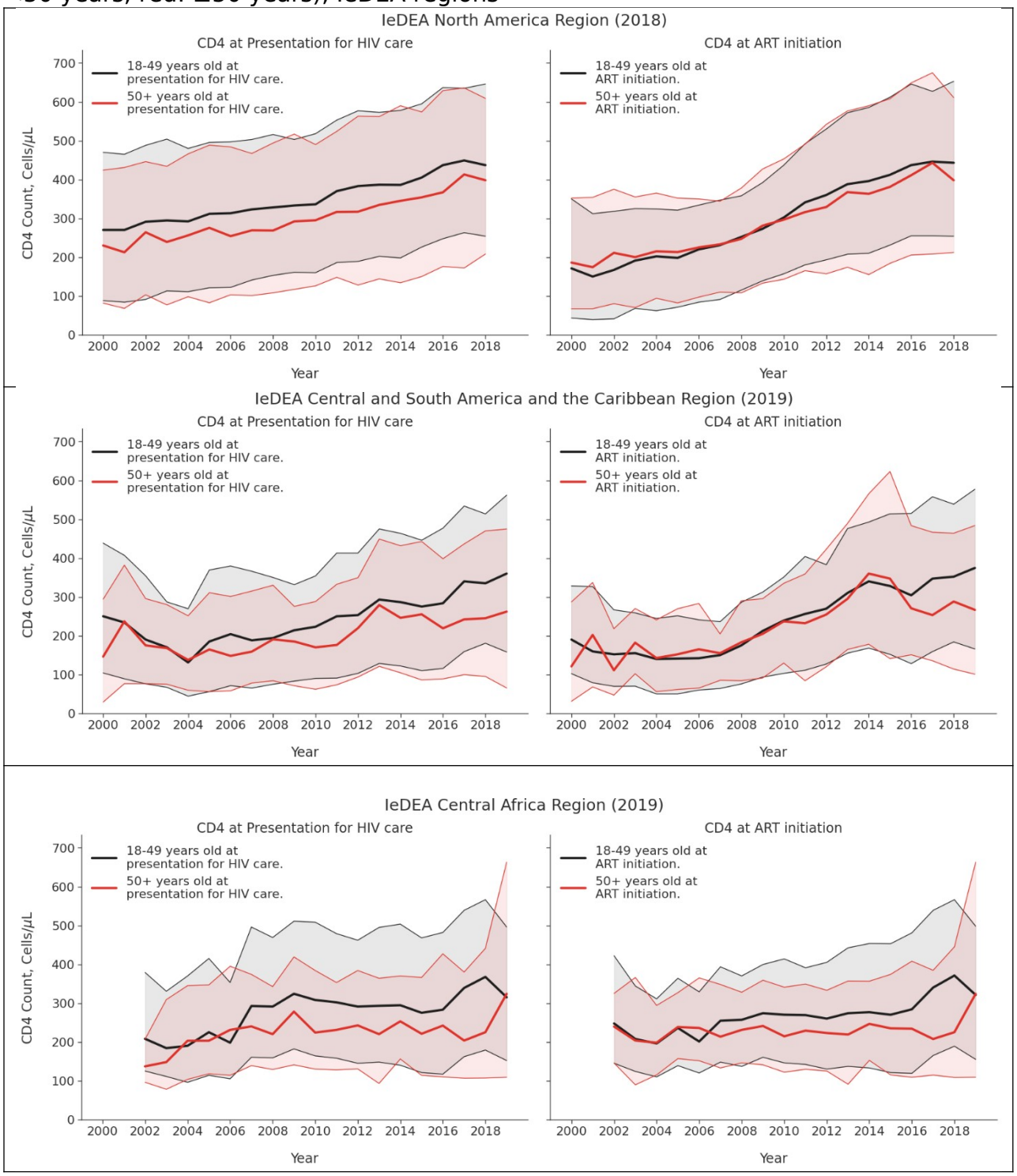
Footnotes:

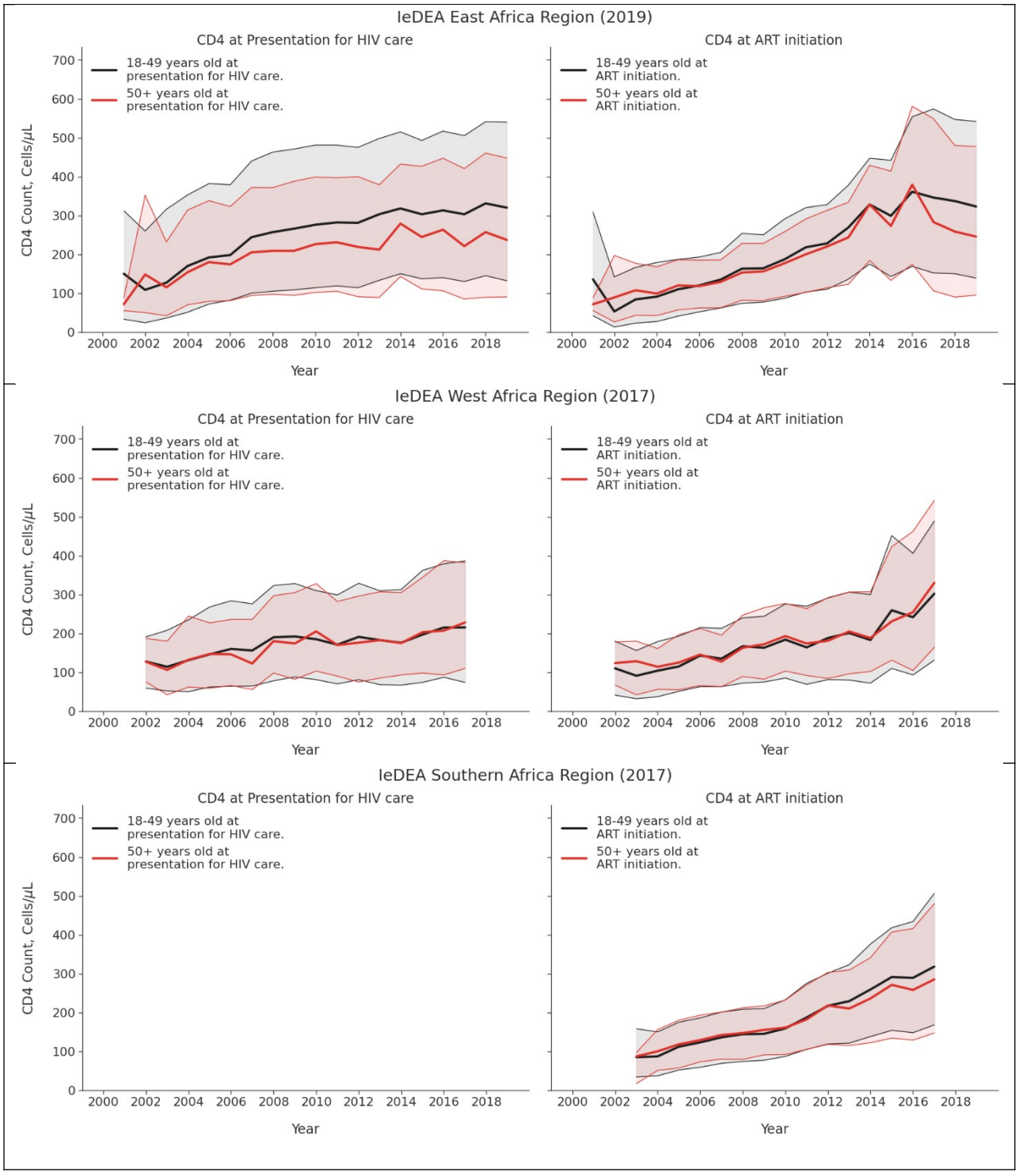
In the IeDEA Southern Africa regional cohort, participants are observed at ART initiation (as opposed to at presentation for HIV care) and then followed forward in time; age at ART initiation is believed to be reflective of age at presentation for HIV care as of 2017 when the “Treat All” guidelines were adopted in Southern Africa.

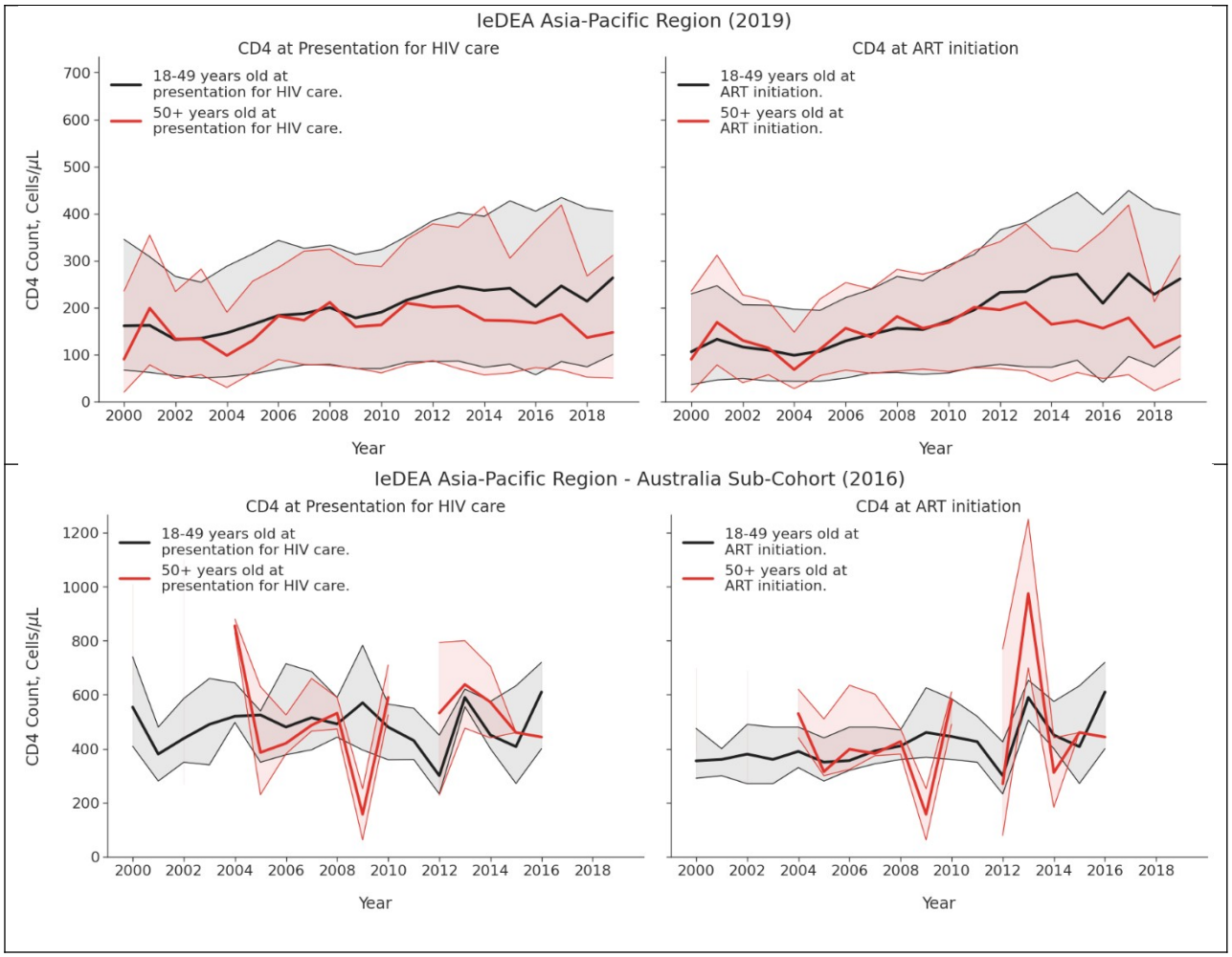
The age at presentation for HIV care in the Australia sub-cohort of IeDEA Asia-Pacific in 2016 is not presented. Participants were recruited to replenish the cohort; the median age at presentation for HIV care is based on a relatively small sub-population (<20 participants) of those presenting for HIV care at participating clinics. Additionally, due to a smaller sample size of women in the Australian sub-cohort, a bandwidth of 3.0 was used for kernel density smoothing.

The kernel density estimation of age distributions was the same as the observed after stratification by sex, with the exception of the age distributions of East African men and women at presentation for HIV care (1 year difference), Southern African women in HIV care (1 year difference), and Australian women in HIV care (2 years difference).

Figure 2: Trends in median (solid line) and interquartile range (shading) of CD4 count at presentation for HIV care (left), and at ART initiation (right), by age (black: <50 years, red: ≥50 years), IeDEA regions




IeDEA East Africa Region (2019)
CD4 at Presentation for HIV care
CD4 at ART initiation
18-49 years old at presentation for HIV care.
50+ years old at presentation for HIV care.
18-49 years old at ART initiation.
50+ years old at ART initiation.
CD4 Count, Cells/μL
Year
IeDEA West Africa Region (2017)
IeDEA Southern Africa Region (2017)



Footnotes:

Estimates of CD4 at presentation for HIV care are not available for Southern Africa. Southern Africa regional cohort observes participants at ART initiation and then follows them forward in time; age at ART initiation is believed to be reflective of age at presentation for HIV care as of 2017 when the “Treat All” guidelines were adopted in Southern Africa.

For additional information regarding policy-influenced changes in CD4 cell count measurement, see Supplement Table 1.

In the Australia sub-cohort of the IeDEA Asia-Pacific region, participants are recruited into the clinical cohort to replenish the cohort in the more recent years; the median age at presentation for HIV care is based on a sub-population (<20 participants) of those presenting for HIV care at participating IeDEA clinics in recent years. Breaks in the line representing CD4 at ART initiation among those 50+ years old at ART initiation signals no individuals 50+ years old initiating ART in the calendar years. The y axis for CD4 count is different for Australia plots (minimum=0 cells/μL, maximum=1250 cells/μL) compared to the other regions (minimum=0 cells/μL, maximum=700 cells/μL)

Table 3: Late presentation (CD4 <350 cells/μL) for HIV care, by age, in the most recent complete calendar year of data available, IeDEA regions

IeDEA Region	N Late Presenters (CD4 <350)	% of <50 years old who were late presenters	% of 50-to-64-year-olds who were late presenters	% of 65+ years-old who were late presenters
Presenting for HIV care				
North America (2018)	500-1,000	38%	42%	47%
Central and South America & the Caribbean (2019)	1-500	49%	61%	60%
Central Africa (2019)	1-500	52%	57%	25%
East Africa (2019)	1,500-2,000	54%	67%	50%
West Africa (2017)	500-1,000	63%	62%	64%
Asia-Pacific (2019)	1-500	69%	81%	75%
Initiating ART (in the Treat All era)				
Southern Africa (2017)	4,500-5,000	55%	62%	50%

Footnotes:
Estimates of CD4 at presentation for HIV care is not available for Southern Africa. In the IeDEA Southern Africa regional cohort, participants are observed at ART initiation (as opposed to at presentation for HIV care) and then followed forward in time; age at ART initiation is believed to be reflective of age at presentation for HIV care as of 2017 when the “Treat All” guidelines were adopted in Southern Africa.
Estimates of CD4 at presentation for HIV care are not presented for the Australia sub-cohort of the IeDEA Asia-Pacific region. Participants were recruited to replenish the sub-cohort in 2016; the median age at presentation for HIV care is based on a relatively small sub-population (<20 participants) of those presenting for HIV care at participating clinics. Presenting estimates would involve subgroups of <5, which breaches confidentiality arrangements.

SUPPLEMENT

Supplement Table 1: Differences in selection, Treat All adoption years, and CD4 measurement clinical practices in the IeDEA regional cohorts. *In 2013, the World Health Organization recommended viral load testing (and not CD4 testing) to monitor virologic failure after ART initiation* [a] *In 2018, the President's Emergency Plan for AIDS Relief (PEPFAR) reduced their support for CD4 testing to prioritize viral load monitoring.* [b] *The IeDEA region has previously shown a decline in pre-ART CD4 testing after adoption of Treat All policies that is steeper in low-and-middle-income countries than in high-income countries.* [c]

IeDEA region	**Selection in to the regional cohort**	**Treat All adoption year (for the majority of countries in the region)**	**CD4 measurement at presentation for HIV care and ART initiation**
North America (NA-ACCORD)	NA-ACCORD contributing clinical cohorts recruit patients at entry into clinical care; this is a dynamic and ongoing process. Contributing cohorts submit data to the NA-ACCORD after the patient successfully links to HIV care, defined as ≥2 HIV clinical visits within 12 months. Data prior to successful linkage to care is not systematically collected on patients, and patients who do not successfully link to care are not included in the NA-ACCORD. The demographics of the NA-ACCORD study population are reflective of all persons with diagnosed HIV in the United States (as reported by the US Centers for Disease Control HIV Surveillance system); demographics are compared annually at www.naaccord.org.	2012	At presentation for HIV care: CD4 measurement has been consistently recommended at presentation for HIV care. At ART initiation: Prior to the adoption of Treat All guidelines, a low CD4 measurement was the predominant stimulus for ART initiation. After the adoption of the Treat All guidelines, ART is initiated regardless of whether a CD4 measurement has occurred. Because guidelines recommend treatment at the time of presentation for care, CD4 is commonly measured at ART initiation and the gap between median CD4 count at presentation for HIV care and at ART initiation has narrowed.[d]
Central and	CCASAnet includes routine clinical cohorts	2014 (Brazil,	The frequency of CD4 cell count testing at

South America and the Caribbean (CCASANet)	from HIV care and treatment clinics in urban centers located in 7 countries: Argentina, Brazil, Chile, Haiti, Honduras, Mexico, and Peru. Participating clinics are principally tertiary, referral care centers except for the clinic in Haiti which provides HIV testing and counselling prior to enrollment. Patients are observed from HIV clinic entry, regardless of prior ART exposure, and are followed until last clinic contact or death.	Mexico), 2015 (Argentina, Chile, Honduras, Peru), 2016 (Haiti)	clinic entry in CCASAnet cohorts has declined from 79% overall in 2015 to 55% in 2019. However, rates of CD4 cell count testing at clinic entry is heterogeneous across clinic sites, ranging from 29% to 94% in 2019.
Central Africa	Central Africa IeDEA includes all patients ever entering care at HIV care and treatment clinics in Burundi, Democratic Republic of Congo, Republic of Congo and Rwanda, along with patients in Cameroon who consented into the study from 2016 onwards. All patients in the Central Africa cohorts are observed from the time of entering HIV care at a participating clinic and are followed until the time of transfer to another site of care, death or loss-to-follow-up.	2016 (Burundi, Cameroon, Rwanda) 2017 (Democratic Republic of Congo), 2018 (Republic of Congo)	Prior to national adoption of WHO's Treat All guidelines, CD4 testing was recommended at presentation for HIV care and prior to treatment initiation, as CD4 counts were used to assess patient immunological status and treatment eligibility, With national adoption of Treat All guidelines, CD4 testing is no longer required for ascertaining treatment eligibility, and is not routinely conducted for all patients.
East Africa	East Africa contributing clinical cohorts include all patients enrolled in clinical care regardless of the number of visits; this is a dynamic and ongoing process.	2016	At presentation for HIV care: CD4 measurement was recommended at presentation for HIV care until the adoption of Treat All guidelines. Thereafter, CD4 was not regularly tested due to lack of reagents. At ART initiation: Prior to the adoption of Treat All guidelines, a low CD4 measurement was the predominant guide for ART initiation. After the adoption of the Treat All guidelines, ART is initiated regardless of whether a CD4 measurement has occurred.
West Africa	Participants are enrolled in the IeDEA West Africa regional cohort at ART initiation. However, data prior to ART initiation such as first visit into HIV care	2016	While most countries in West Africa have adopted Treat All guidelines in 2016, it has translated into a heterogeneous situation; some countries experiencing a significant

	are also available.		decline in CD4 measures at ART initiation such as Côte d'Ivoire while other have maintain a high proportion of CD4 measures after adoption of Treat All.
Southern Africa	Participants are observed in the IeDEA Southern Africa region at ART initiation (as opposed to presentation for HIV care) and then are observed moving forward in time.	2017	As previously shown, the frequency of CD4 testing plateaued or declined in Southern African IeDEA-contributing cohorts after 2010; this was reflected in a decline in the percentage of participants who had a CD4 cell count at ART initiation from 78% in 2008 to 40% in 2017.
Asia-Pacific	Participants are enrolled into the IeDEA Asia-Pacific regional cohort (excluding Australia) from two groups: 1) dynamic clinical cohorts that enroll all those seeking clinical care; and 2) closed clinical cohorts that recruit patients to replenish the cohort when participants die, transfer, or are loss to follow-up.	2017-2018	CD4 measurements at presentation for HIV care have been recommended. When ART initiation was distant from entry into HIV care, a repeat CD4 within 6-12 months from the prior test would have been preferred. In the context of the analysis presented in this paper, 34% of those who started ART did not have a CD4 count at ART initiation.
Australia sub-cohort of Asia-Pacific region	Participants were largely enrolled into the Australia sub-cohort from clinical care sites from 1999 to 2002, and between 2009 and 2012. In intervening and subsequent years, recruitment of new participants occurs to replenish the cohort when participants die, transfer, or are loss to follow-up	2015	Under Australian antiretroviral treatment guidelines, CD4 testing is recommended at entry into care and prior to treatment initiation.

a. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Geneva: World Health Organization; 2013. Available at: https://www.who.int/hiv/pub/guidelines/arv2013/en/

b. Kaiser Family Foundation. The U.S. government engagement in global health: a primer. 2019. Available at: https://www.kff.org/report-section/the-u-s-government-engagement-in-global-health-a-primer-report/
c. Brazier E, et al. Effect of national adoption of Treat-All guidelines on pre-ART CD4 testing and viral load monitoring after ART initiation: A regression discontinuity analysis. Clin Infect Dis 2021;ciab222
d. Lee JS, et al. CD4 count at entry into HIV care and at antiretroviral therapy prescription in the US, 2005-2018. Clin Infect Dis 2020;ciaa1904.
e. Zaniewski E, et al. Trends in CD4 and viral load testing 2005-2018: multi-cohort study of people living with HIV in Southern Africa. J Int AIDS Soc 2020;23(7):e25546.

TO BE POSTED ON IeDEA YouTube Channel

Figure: Changes in age at presentation for HIV care distribution, and age distribution of those in HIV care, 2000-the most recent complete calendar year of data available, IeDEA regions

.mp4 files have been posted to the IeDEA Hub for your review

Footnotes:
In the IeDEA Southern Africa regional cohort, participants are observed at ART initiation (as opposed to at presentation for HIV care) and then follows them forward in time; age at ART initiation is believed to be reflective of age at presentation for HIV care as of 2017 when the “Treat All” guidelines were adopted in Southern Africa.
The age at presentation for HIV care in the Australia sub-cohort of IeDEA Asia-Pacific is not presented. Participants were recruited into to replenish the cohort; the median age at presentation for HIV care is based on relatively small sub-population (<20 participants) of those presenting for HIV care at participating clinics.

Figure: Changes in age at presentation for HIV care distribution and age distribution of those in HIV care, by sex, 2000-the most recent complete calendar year of data available, IeDEA regions

.mp4 files have been posted to the IeDEA Hub for your review

Footnotes:
In the IeDEA Southern Africa regional cohort, participants are observed at ART initiation (as opposed to at presentation for HIV care) and then follows them forward in time; age at ART initiation is believed to be reflective of age at presentation for HIV care as of 2017 when the “Treat All” guidelines were adopted in Southern Africa.
The age at presentation for HIV care in the Australia sub-cohort of IeDEA Asia-Pacific is not presented. Participants were recruited into to replenish the cohort; the median age at presentation for HIV care is based on relatively small sub-population (<20 participants) of those presenting for HIV care at participating clinics.
Additionally, due to a smaller sample size of women in the Australian sub-cohort, a bandwidth of 3.0 was used for kernel density smoothing.