Ageing with HIV

Delayed presentation of HIV among older individuals: a growing problem

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Late presentation for care is a major impediment to the prevention and effective treatment of HIV infection. Older individuals are at increased risk of late presentation, represent a growing proportion of people with late presentation, and might require interventions tailored to their age group. We provide a summary of the literature published globally between 2016–21 (reporting data from 1984–2018) and quantify 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 2000–19, encompassing four continents. Finally, we consider how late presentation among older individuals might be more effectively addressed as electronic medical records become widely adopted.

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This is the third in a Series of four papers about ageing with HIV (papers 1 and 2 appear in *The Lancet Healthy Longevity*)

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Introduction

The successful scale-up of effective antiretroviral therapy (ART) has supported the long-term survival of people with HIV infection. More people than ever are living with HIV, and this population is ageing.[1–4] Globally, UNAIDS has estimated that the total number of people older than 50 years with HIV infection has increased from 5·4 million to 8·1 million between 2015 and 2020. In this four-part series, we explore pressing issues facing older people with HIV in the era of ART. In this Series paper, we address the risk of delayed presentation for ART.

In many settings, the prevalence of HIV among older individuals and number of new infections in this age group has increased. Between 2015 and 2019 in the USA, the overall prevalence of people with HIV infection increased by 8% and incident infections decreased by 4%.[5] In contrast, among people 50 years and older, there was a 40% increase (from 289 900 to 407 100) in prevalence and 15% increase (from 2700 to 3100) in incidence—the largest increases of any age group.[5] This increase is likely to be due to intragenerational and crossgenerational condomless sexual activity.[6,7]

Large-scale population-based statistics on HIV incidence in older age groups are sparse outside of the USA, but some data are available from South Africa. By the end of 2013 in South Africa, 6304 (14%) of 44 909 people with HIV infection in care were aged 50 years or older.[8] Among 84 078 patients starting ART from 2004 to 2013, the proportion of those aged 50 years or older increased from 290 (6%) of 4999 in 2004 to 961 (10%) of 9657 in 2012–13.[8] In another study that tested a cohort of 1360 individuals aged 40 years or older for HIV in 2010 and retested in 2015, HIV prevalence increased from 21% to 23%, corresponding to 33 incident infections (0·49 infections per 100 person-years); only those aged 80 or older had no new infections.[6]

12 years ago, we used data from the USA and Canada to compare CD4 cell count and AIDS-defining conditions (eg, recurrent bacterial pneumonia, Kaposi's sarcoma, or typical or atypical mycobacterium infections) at presentation for HIV care among individuals younger than 50 years with that of individuals aged 50 years or older.[9] Older individuals had lower CD4 counts and a higher prevalence of AIDS-defining conditions at diagnosis, and these gaps between younger and older people at presentation persisted over time despite decreases in new diagnoses among both groups.[9] Now that an even larger proportion of individuals living with HIV are aged 50 years and older worldwide, we revisit the relationship between age and delayed presentation for care globally.

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 aged 50 years or older, and nearly half of them have delayed presentation
- In many regions of the world, the age-associated gap in CD4 count at presentation is widening as the average CD4 count at presentation rises for younger adults
- Few studies have focused on factors associated with late presentation specifically for older individuals
- Early diagnosis and treatment of HIV for older individuals is particularly challenging because early signs and symptoms might be attributed to diseases of ageing and because neither these individuals or their care providers perceive them to be at risk of HIV infection
- If the widening age-associated CD4 gap is to be addressed, interventions will need to be explicitly targeted to older individuals

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See **Online** for appendix

Review of recent literature

We conducted a structured review of literature published in 2015–21 (appendix pp 1–3). These studies were done in Africa, Asia, Australia, Europe, the Middle East, North America, and South America and include observations from 1984 through to 2018. Most studies (32 of 40) defined late presentation as having a CD4 count of fewer than 350 cells per µL or an AIDS diagnosis at or near the time of presentation for care. Although these studies documented improvements in recent years, delayed presentation remains a substantial global issue in HIV care. In many settings, approximately half of people newly diagnosed with HIV infection have CD4 counts of less than 350 cells per µL at presentation, and this proportion is even higher in lower-income and middle-income countries.

Older age was variably defined (sometimes as young as ≥35 years but usually defined as ≥50 years old), but older age was consistently associated with delayed presentation. Relative risk (which we typically measured using adjusted odds ratios [ORs], but in some cases, we calculated unadjusted ORs from data provided) for delayed presentation associated with older individuals compared with younger individuals (variably defined as <35 years or <20 years) ranged from 1·1 to 7·4.

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.[10] Gesesew and colleagues[10] studied 4900 people presenting for care at a single site in southwestern Ethiopia and found that people aged 50 years and older were less likely to have a delayed presentation than were people aged 15–24 years (hazard ratio [HR] 0·4; 95% CI 0·3–0·6). Another study done in Italy separated Italians from non-Italians and found that, compared with people aged 35–49 years, Italians older than 50 years were at increased risk of delayed presentation (HR 1·5; 1·4–1·7) but non-Italians aged 50 years were not (0·9; 0·7–1·2).[11]

Some of these studies considered whether there had been opportunities for earlier diagnosis and whether these differed by age.[12–16] These studies documented more missed opportunities for diagnosis among older individuals than among younger individuals.

IeDEA data

To add a recent and standardised accounting of delayed presentation for HIV care around the world, we present data from the International epidemiology Databases to Evaluate AIDS (IeDEA) global consortium. IeDEA harmonises data on care and treatment of people with HIV from seven international regional data centres, including four in Africa, one in the Asia-Pacific region (which includes an Australia subcohort), one in the Central America, South America, and Caribbean region (also includes Mexico, Haiti, and Honduras), and one in North America (the USA and Canada). Each region contributed aggregated data from adults (aged ≥18 years) to the Epidemiology and Biostatistics Core of the North American AIDS Cohort Collaboration on Research and Design, the North American region of IeDEA, where the figures presented were created. In most regions, cohorts are ongoing and include individuals presenting for HIV care, with the exception of cohorts in the Southern Africa and Asia-Pacific regions. In the Southern Africa IeDEA region, participants enter into observation at the initiation of ART, which can occur after presentation for HIV care; this region did not contribute to data of people presenting for HIV care. The Asia-Pacific region data combined two approaches to cohort enrolment—selectively enrolling patients to replace participants who had died, were transferred, or were lost to follow-up (including all Australian subcohort sites), or enrolling all patients seen at the site. The results presented might 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 use sampling strategies for representativeness. Additional information regarding the selection of participants for enrolment into the IeDEA regional cohorts, the adoption of guidelines to provide HIV treatment regardless of CD4 count (ie, Treat All guidelines), and the changes in CD4 testing that influence the results presented in this Series paper can be found in the appendix (pp 4–6) and a recent global IeDEA study.[17]

We defined three study populations. First, the population of individuals observed to present for HIV care at an IeDEA-contributing clinical care site was restricted to individuals for whom there was no evidence of a previous HIV care visit, no history of ART, and no 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 encounter with HIV care. Third, the study population of individuals presenting for HIV care were additionally restricted to those who were observed to initiate ART at, or after, presentation for care.

The CD4 cell count at presentation for HIV care was the closest measurement to presentation for care, measured within a window of 12 months before to 12 months after enrolment; if ART was initiated within 12 months after enrolment, the window was shortened to 7 days after ART initiation. The CD4 cell count at ART initiation was the closest measurement to ART initiation, measured within a window of 12 months before to 7 days after ART initiation.

Histograms were created for each region to visualise the age distribution at presentation for care, and in the most recent complete calendar year of data. A kernel density smoothing bandwidth of 2·0 was used to visualise the age distribution histograms. Animated age distributions that visualise these changing age distributions

during the past two decades can be found on the IeDEA YouTube channel. The proportion of adults presenting for HIV care was estimated within age groups (<50 years, 50–64 years, and ≥65 years) among the total presenters for HIV care.

In 2013, WHO recommended viral load testing (and not CD4 testing) to monitor virologic failure after ART initiation.[17–20] In 2018, the President's Emergency Plan for AIDS Relief reduced their support for CD4 testing to prioritise viral load monitoring.[19] IeDEA has previously shown a decline in pre-ART CD4 testing after the adoption of Treat All policies that is steeper in low-income and middle-income countries than in high-income countries.[17] 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 (<50 years 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 of fewer than 350 cells per µL at presentation for care were considered to have late presentation. The proportion of adults with late presentation was estimated within each age category (<50 years, 50–64 years, 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: 2018 in North America; 2019 in Central America, South America, and the Caribbean; 2019 in Central Africa; 2019 in East Africa; 2017 in West Africa; 2017 in Southern Africa; and 2019 in the Asia-Pacific region (2016 in the Australia subcohort).

Age in IeDEA regions

The proportion of adults in HIV care who are aged 50 years or older is substantial throughout IeDEA regions, ranging from 17% in southern Africa to 50% in North America (figure 1). The proportions of women and men in care who are 50 years or older are similar between the North America region and Central America, South America, and

For more on the **IeDEA YouTube channel** see https://www.youtube.com/channel/UC9cfdwlBl944eQ9AGj1EOkw

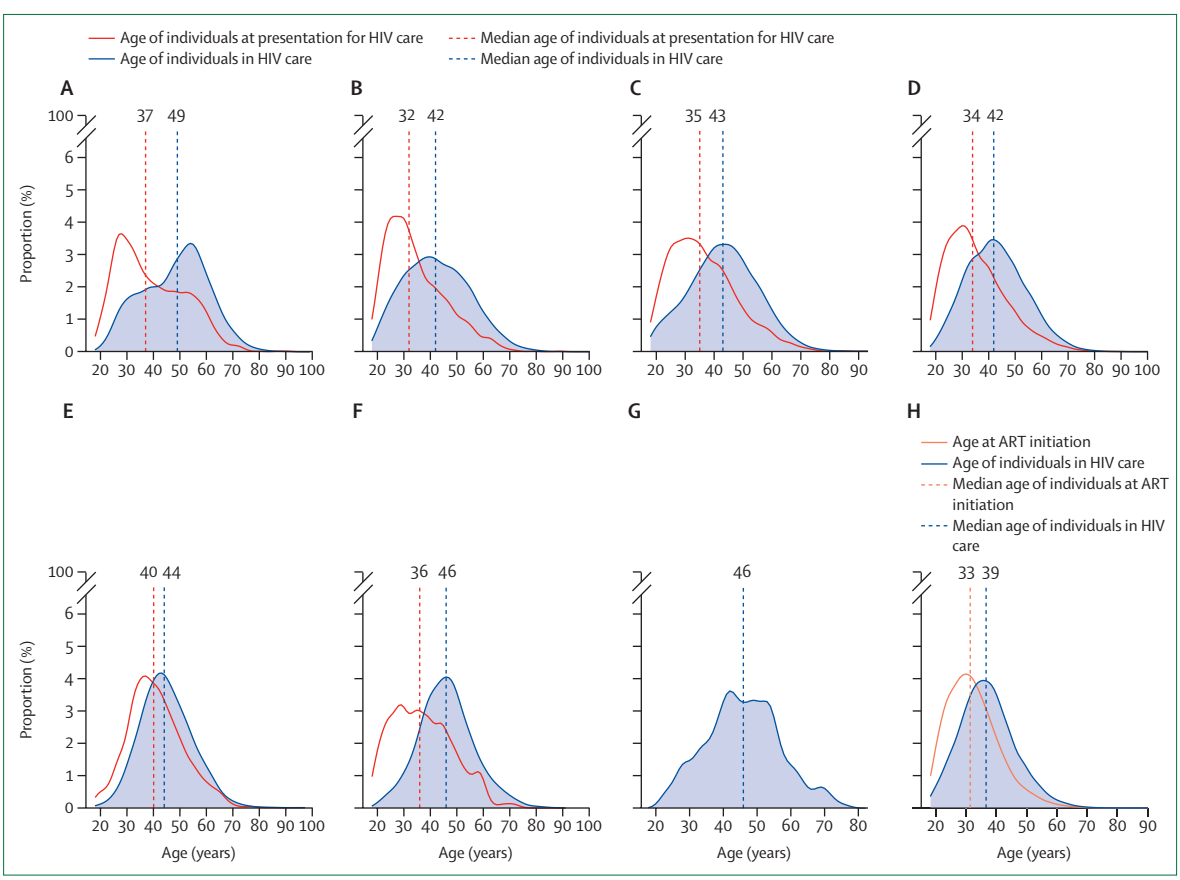


Figure 1: **Age at presentation for HIV care and age among all those in HIV care in IeDEA regions**
(A) North America region (2018). (B) Central America, South America, and the Caribbean region (2019). (C) Central Africa region (2019). (D) East Africa region (2019). (E) West Africa region (2017). (F) Asia-Pacific region (2019). (G) Asia-Pacific region Australia subcohort (2016). (H) Southern Africa region (2017). In the IeDEA Southern Africa regional cohort, participants were observed from ART initiation (not from presentation for HIV care); 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 subcohort of IeDEA Asia-Pacific in 2016 is not presented because the median age at presentation for HIV care was based on a relatively small subpopulation (<20 participants) of those presenting for HIV care. Participants were recruited to replenish the Australian subcohort in 2016. ART=antiretroviral therapy. IeDEA=International epidemiology Databases to Evaluate AIDS.

	Range of the number presenting for care	Proportion of people aged <50 years at presentation (%)	Proportion of people aged 50–64 years at presentation (%)	Proportion of people aged ≥65 years at presentation (%)
North America (2018)	1000–1500	76%	21%	3%
Central America, South America, and the Caribbean (2019)	1000–1500	89%	10%	1%
Central Africa (2019)	1500–2000	87%	11%	2%
East Africa (2019)	10 000–10 500	88%	10%	2%
West Africa (2017)	1000–1500	81%	17%	2%
Asia-Pacific (2019)	500–1000	84%	14%	1%
Southern Africa (2017)	22 000–22 500	93%	7%	1%

Estimates of age at presentation for HIV care are not presented for the Australia subcohort of the IeDEA Asia-Pacific region. Participants were recruited to replenish the Australian subcohort in 2016; the median age at presentation for HIV care is based on a small subpopulation (<20 participants) of those presenting for HIV care at participating IeDEA clinics. Presenting estimates in these age groups would involve subgroups of less than five participants, which breaches confidentiality arrangements. In the IeDEA Southern Africa regional cohort, participants are observed from ART initiation (not from presentation for HIV care); 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. ART=antiretroviral therapy. IeDEA=International epidemiology Databases to Evaluate AIDS.

Table 1: **Age at presentation for HIV care by IeDEA regions**

Caribbean region; however, a lower proportion of women who are 50 years or older are in HIV care than men in this age group in the African and Asia-Pacific (including the Australian subcohort) regions (appendix p 7).

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

Although the differences vary by IeDEA region, in nearly every region, people with HIV infection who were 50 years or older were presenting with lower CD4 counts than their younger counterparts (figure 2). Even more concerning, in many regions (Central America, South America, and the Caribbean, Central Africa, East Africa, and the Asia-Pacific regions), the gaps are widening with time as the average CD4 count at presentation rises in younger adults presenting for care.

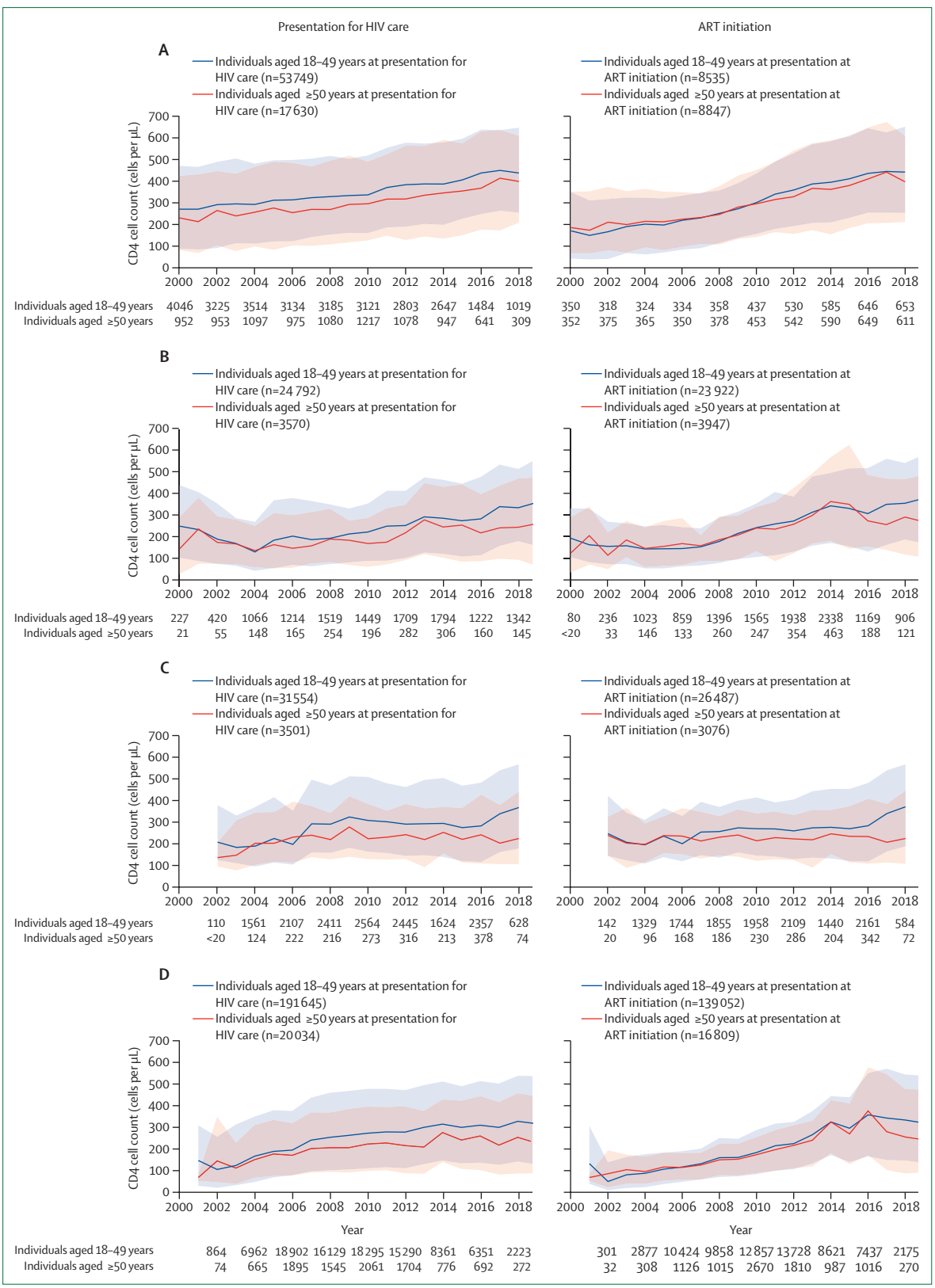
Recent IeDEA data (table 2) support findings from the structured review of the literature (appendix pp 1–3). People aged 50 years or older were substantially more likely to have late presentation for care than people younger than 50 years. In most regions, the majority of people who were 50 years or older presented late to care.

A troubling cycle

Older people are increasingly presenting for HIV care. Some of these individuals were recently infected, but a disproportionate number have had a substantial delay in diagnosis. Although it is known that CD4 counts decline with age among uninfected individuals,[21] these disparities in CD4 count at presentation are unlikely to be explained by the biology of ageing alone. The gap between people presenting at a young age and those presenting at an older age appears to be widening in much of the world as the average CD4 count at presentation is increasing at a faster rate among populations of younger adults who are often targeted for test-and-treat strategies. Furthermore, a natural decline in CD4 counts and accentuated ageing with HIV[22] only underscores the need for earlier diagnosis and treatment for older individuals.

We are concerned that a troubling cycle could be developing. The life expectancy of the world's population is increasing in general, increasing the absolute number of older individuals.[23] With increased life expectancy, older individuals are continuing to enjoy sexual activity,[24–26] which might be both intragenerational 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 people being beyond child-bearing age all contribute to inconsistent use of condoms,[28,29] increasing opportunities for HIV transmission. This increase in opportunities for transmission is concerning because older people with HIV infection have delayed presentation for HIV treatment compared with younger people, prolonging the period in which they could expose others to infection. Delayed presentation also decreases their ability to benefit from early initiation of ART.[8,30] Increased HIV incidence among older individuals also increases prevalence. 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.[31] No single intervention will fix this problem. Each country and health system will need to consider which of the following 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, and discussion of the pros and cons of pre-exposure prophylaxis (PrEP) among older adults who are at risk of HIV infection.



(Figure 2 continues on next page)

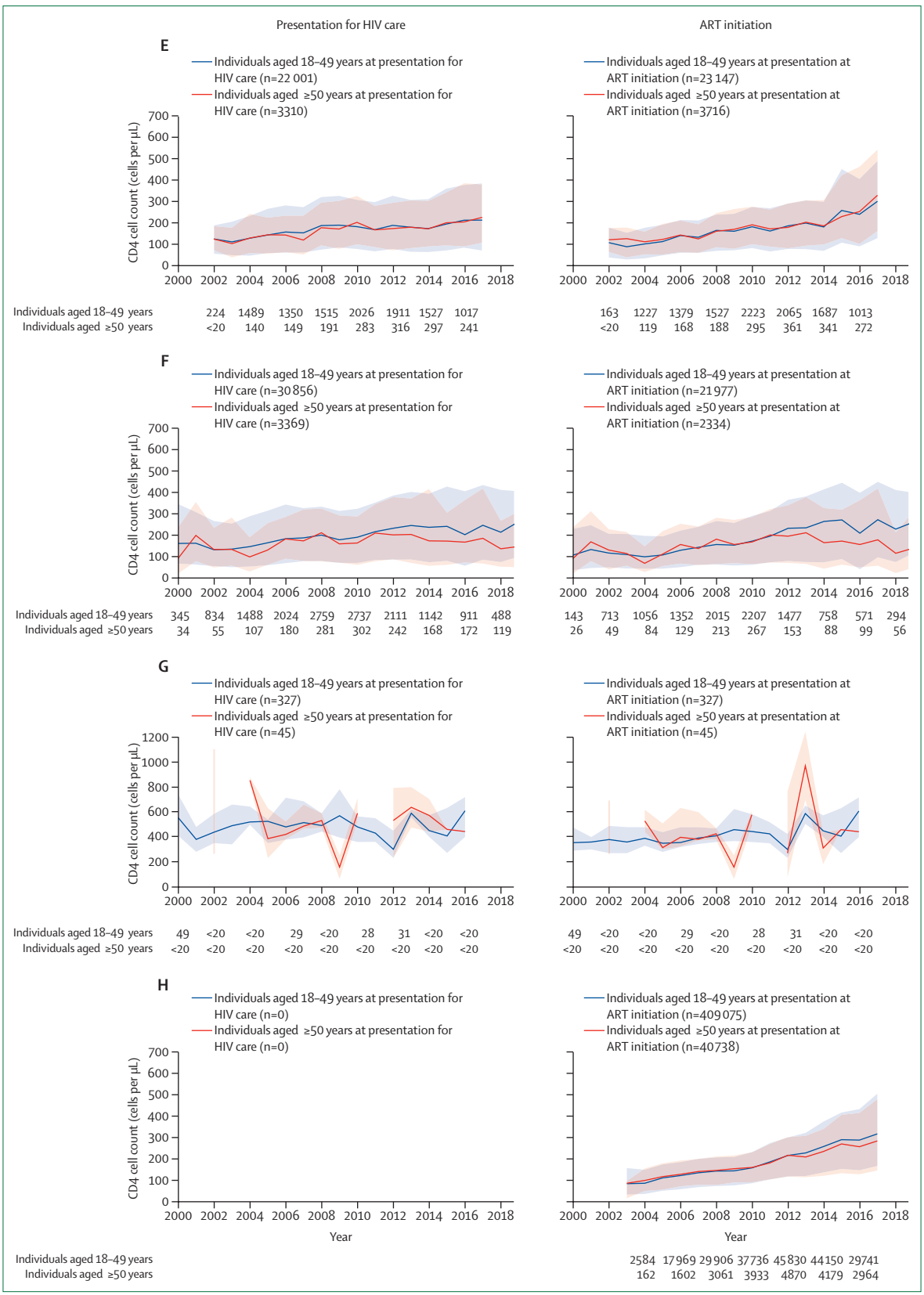


Figure 2: **Median CD4 cell count per year by age group at presentation for HIV care and at ART initiation in IeDEA regions**
(A) North America region (2018). (B) Central America, South America, and the Caribbean region (2019). (C) Central Africa region (2018). (D) East Africa region (2019). (E) West Africa region (2017). (F) Asia-Pacific region (2019). (G) Asia-Pacific region Australia subcohort (2016). (H) Southern Africa region (2017). The total number of people contributing to the estimates in each year, by age (18–49 years and ≥50 years) are noted for the calendar years labelled on the x axis. The plots for Central Africa end in 2018 due to the decrease in CD4 cell count measured in 2019 (the last complete calendar year of data available from the Central Africa region). Estimates of CD4 cell count at presentation for HIV care are not available for Southern Africa. The Southern Africa regional cohort observes participants starting from ART initiation; 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. In the Australia subcohort of the IeDEA Asia-Pacific region, participants were recruited into the clinical cohort to replenish the cohort; the median age at presentation for HIV care was based on a subpopulation (<20 participants) of those presenting for HIV care at participating IeDEA clinics between 2000 and 2016. Breaks in the line representing CD4 cell count at ART initiation among those older than 50 years old shows that no individuals older than 50 years initiated ART in that year. The y axis for CD4 count is different for the Australian subcohort compared with the other regions. ART=antiretroviral therapy. IeDEA=International epidemiology Databases to Evaluate AIDS.

Interventions for older adults

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 quality-adjusted life-year (QALY) threshold of US$50 000, suggest that screening is justified in any population with a threshold of 0·1% or greater undiagnosed HIV prevalence.[32–34] Recent work that considered more recent and durable ART, adoption of test and treat strategies, and a $100 000 QALY standard found routine testing to be cost-effective at diagnostic rates of 0·01% or more.[35] This threshold is met (or surpassed) among people aged 65 years or older in many settings. For example, in South Africa, the prevalence of HIV in people aged 50 years or older (7·1%) easily justifies universal screening, yet only 54% of those aged 50 years or older reported ever testing for HIV, compared with 78% of people aged 25–49 years.[36] Furthermore, the cost of HIV screening continues to decrease, which could lower the threshold for universal screening. However, US Centers for Disease Control and Prevention guidelines for one-time universal screening remain restricted to people aged 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 US Veterans Health Administration in 2009, new HIV diagnoses were established in 0·14% of 210 957 people tested from 2009 to 2012 compared with 0·46% of 89 652 tested from 2006 to 2009 under risk-based testing.[38] Overall, people aged 65 years or older did not cross the 0·1% threshold for screening (new HIV diagnoses in people aged 65–74 years were 0·07% [95% CI 0·02–0·09%] and 0·02% [0·01–0·03%] in people aged ≥75 years).[38] However, corresponding with societal inequities, some populations are at greater risk than others and circumstances exist in which universal screening of people aged 65 or older is justified. The investigators found that rate of new diagnoses among Black patients was 0·16% (0·07–0·24%) for those aged 65–74 years and 0·09% (0·00–0·19%) for those aged 75 years or older.[38] 10 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 within the Veterans Healthcare System aged 65–74 years.[38,39] It is not known what we would see now if the study was repeated.

There are special reasons to shift away from risk-based testing for older individuals. This testing would be less stigmatising if HIV testing was the default.[40] In many countries, older individuals are not viewed by health-care providers, nor do they see themselves, as at risk for HIV. Older individuals might also be concerned that their privacy will not be protected, making them less likely to request testing or to present where testing is provided.[40] Furthermore, although all sexual minorities face challenges in having discussions of risk behaviour with their providers, older sexual minorities face the combined stigma of age and sexual minority status.[41] Finally, previous studies have convincingly shown the value of normalising HIV testing,[42] possibly by including HIV testing as part of an array of tests for common age-associated illnesses.

	Range of the number of people with late presentation (CD4 count <350 cells/μL)	Proportion of people aged <50 years with late presentation (%)	Proportion of people aged 50–64 years with late presentation (%)	Proportion of people aged ≥65 years with late presentation (%)
North America (2018)	500–1000	38%	42%	47%
Central and South America and the Caribbean (2019)	1–500	49%	61%	60%
Central Africa (2019)	1–500	52%	57%	25%
East Africa (2019)	1500–2000	54%	67%	50%
West Africa (2017)	500–1000	63%	62%	64%
Asia-Pacific (2019)	1–500	69%	81%	75%
Southern Africa (2017)	4500–5000	55%	62%	50%

Estimates of CD4 at presentation for HIV care are not presented for the Australia subcohort of the IeDEA Asia-Pacific region. Participants were recruited to replenish the subcohort in 2016; the median age at presentation for HIV care is based on a relatively small subpopulation (<20 participants) of those presenting for HIV care at participating clinics. Presenting estimates would involve subgroups of less than five participants, which breaches confidentiality arrangements. In the IeDEA Southern Africa regional cohort, participants were observed from ART initiation (not from presentation for HIV care); 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. ART=antiretroviral therapy. IeDEA=International epidemiology Databases to Evaluate AIDS.

Table 2: **People with late presentation (CD4 <350 cells per μL) for HIV care, by age, in the most recent complete calendar year of data available in IeDEA regions**

HIV self-testing

In the USA, nearly 40% of new HIV infections are transmitted by people who do not know that they are living with HIV, and these proportions might be higher in countries where testing is less accessible.[37] However, stigma, fear of isolation from friends and family, and poor HIV health literacy are particularly strong among older people with HIV.[43,40] Furthermore, older individuals are more likely to have established linkages to care for other chronic conditions than are younger individuals.[31] Although these pre-existing conditions might make it more probable that physicians will misattribute signs of HIV infection, it could 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 as it could empower them to first learn their diagnosis and then choose where to seek care.[44] Self-testing might be even more beneficial for older individuals who are concerned about privacy or are sexual minorities.[40,45] Research has begun to identify ideal characteristics of HIV self-tests[46] and, in Agincourt, South Africa, home testing is already available.[40] Similarly, expanding point-of-care accessibility for testing in resource-constrained settings makes sense, so long as a clear linkage to care is possible.[47]

Routine clinical discussion of sexual health and substance use

Guidelines recommend annual testing for anyone with active risk behaviours,[37] but providers are often unaware of ongoing substance use or condomless sex among their older patients, and they rarely ask.[48,49] Health-care providers are particularly uncomfortable discussing sexual behaviours with older people who are sexual minorities.[41] One study characterised 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".[50]

Older individuals continue to be sexually active, some with multiple intragenerational and crossgenerational partners[7] and many continue to use alcohol and other substances with multiple implications for their health and wellbeing, including their risk of HIV infection.[24,27,51] As lifespan has extended, so has sexual healthspan and ongoing sexual activity into older age.[51,52] In South Africa, this increase in sexual activity into older age is particularly true for men who report continuing to have sex with their wives and with younger unmarried women.[7] Furthermore, the historic cohort of individuals currently aging with HIV in upper-income 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 might 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.[24,25,51,52] Older men and women face challenges to continuing sexual activity, including erectile dysfunction for men and vaginal dryness for women, both of which are addressable problems. Erectile dysfunction can make use of a condom difficult, if not impossible.[28,29] Furthermore, most older people welcome discussion of their sexuality with their health-care providers, but they prefer that the provider raise the issue.[24,51,52] By raising the question of sexual health in a non-threatening and non-stigmatising manner, the provider can create a safe environment to discuss sexual risk behaviors and HIV.

Compelling reasons exist 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 crucially important health implications, including risk of cancer,[53] liver disease,[26] metabolic disease,[54] interaction with prescription medications,[55] risk of falls and fractures,[56] and cognitive decline.[57] Non-injection drug use, including alcohol use, increases disinhibition and leads to high-risk behaviours, including sex with multiple partners and condomless intercourse.[58,59] When disinhibition is combined with erectile dysfunction and a little perceived concern regarding pregnancy, condoms are rarely used. 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.[60] Along with multiple sexual partners and injection drug use, non-injection drug use, including unhealthy alcohol use, should be considered as a risk behaviour 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.[61–64] The underlying premise of using indicator conditions is that some conditions should be considered indications for HIV testing, regardless of disclosed risk behaviours. These conditions fall into three general categories—namely, indicators of risk behaviours that might be undisclosed, indications of early symptomatic HIV disease, and possible indicators of advanced HIV disease. Identified indicators of undisclosed risk behaviours include viral hepatitis and any sexually transmitted infections. Indicators of possible early symptomatic HIV disease include persistent influenza-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 infection include cervical cancer, unexplained neuropathy, weight loss, or dementia—although these should always trigger HIV testing, they often occur up to 10 years after initial infection. Tuberculosis also indicates advanced HIV infection but can occur much earlier than other possible advanced HIV disease indicators.

Unfortunately, indicator conditions that might trigger HIV testing among younger individuals can be attributed to other causes in older individuals. In 2007, we published a study using the US Veterans Administration data, showing that veterans already in Veterans Administration care before their HIV diagnosis were no more likely to be diagnosed early in the course of their disease than those newly entering Veterans Administration care.[65] Furthermore, only a few of these patients had an indicator condition before their diagnosis. Recently, there has been renewed interest in the use of trigger conditions and these studies have confirmed and extended our findings. These studies underscore that trigger conditions are more common among older individuals, but prompt HIV testing in this age group less often than in younger individuals.[61–64]

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 Australasia, few things are further from their clinical focus. Even in countries with higher HIV prevalence and greater general awareness, providers might not consider testing older individuals who they deem to be at lower risk. In this context, 20 years of fully paperless, national, electronic medical records in the US Veterans Healthcare System might offer important insights.[50,66–69] Electronic health record clinical reminders might help overcome documented failures of one-time universal screening and risk-based and indicator condition-based testing.

When effectively implemented and maintained, universal screening can provide more timely diagnoses of HIV infection. In August, 2009, the US Veterans Health Administration 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 Veterans Administration.[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.[50] The intervention included an electronic clinical reminder, a multifaceted provider activation programme, social marketing to providers and patients, regular informal conversations with providers, and quarterly feedback on rates of testing.[50] The proportion of newly diagnosed people aged 60 years or older increased from 7·5% to 15·3% (p=0·10) after the intervention was implemented and the proportion of patients with CD4 cell counts of fewer than 200 cells per µL (well below the more commonly-used late presenter threshold of <350 cells per µL) decreased from 43% to 29% (p=0·04).[50] A facility that implemented only the electronic reminder linked to a test order had the same improvement in testing as a facility with the full multimodal intervention, suggesting that this was the element most crucial to success.[70] Similarly, clinical prompts could also improve adherence to risk-based and indicator condition testing.

For settings with limited resources, innovative approaches using solar power,[71] cloud-based systems,[72] and mobile phone applications[73] for data entry have been developed to support electronic health records in the context of intermittent, or non-existent, electricity. These approaches have been successfully used in Kenya,[74] India,[75] and other low-income to middle-income countries.[76] They have already demonstrated effectiveness at improving the timing of ART in Kenya.[72]

Discussion of pros and cons of PrEP among older adults at risk of HIV

Among those at substantial risk of HIV infection, a frank discussion of the pros and cons of PrEP, tailored to older adults, 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.[77] However, the addition of two antiretrovirals (a combination of emtricitabine [200 mg] and either tenofovir disoproxil fumarate [300 mg] or tenofovir emtricitabine [25 mg]) to a medication regimen that might already cross the line into polypharmacy (ie, ≥5 chronic medications) might result in increased risks of hospitalisation and mortality.[78] Polypharmacy is a growing problem among older individuals[79] and the long-term safety of these medications in individuals aged 65 years and older is largely unknown.[80]

Tenofovir disoproxil fumerate is associated with nephrotoxicity and is contraindicated for people with a creatinine clearance of less than 60 mL/min.[81,82] Tenofovir disoproxil fumerate is also associated with bone loss and can contribute to osteoporosis,[81,82] a particular concern among older individuals, especially women. However, for either preparation of PrEP, a careful consideration of what other medications the individual is taking and whether these toxicities might exacerbate those of the other medications is indicated.[80]

Furthermore, 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 monitoring might seem like too much additional effort to patients who might only have sexual intercourse or use injection drugs intermittently.[83]

Momentum is building for on-demand PrEP.[82,84,85] IPERGAY randomly assigned men who have sex with men to receive pericoital PrEP—two pills between 2 h and 24 h before anal intercourse and one pill daily for 2 days after sex but no more than seven pills in a single week. Pericoital PrEP might substantially curtail

Search strategy and selection criteria

We searched PubMed using the search terms ("late presentation" or "delayed diagnosis") and "HIV" and restricted to manuscripts published in English (at least in part) between May 20, 2015, and May 19, 2021. We required that the publications be original research, include an adult population (aged older than 15 years), define late presentation, and adequately characterise the sample evaluated, including sample size, region, and calendar period from which the sample was drawn, and the proportion or number of people who presented late. A review of titles and abstracts eliminated all but 74 publications. These manuscripts were additionally restricted to articles reporting the association of age with late presentation and the number was reduced to 40.

concerns about toxicity. Although pericoital PrEP might be an appealing solution, additional work is needed to determine the efficacy of this dosing strategy in other populations.

Conclusion

Although older individuals more often present for HIV care late and have more contact with the health-care system, few studies have focused on factors associated with late presentation specifically among older individuals. This focus is important because older age is independently associated with risk of 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 assess how best to implement more widespread testing and earlier diagnosis and treatment in this growing age group.

Contributors

ACJ contributed to the conceptualisation, investigation, project administration, writing, and editing; KNA contributed to the data curation, methodology, supervision, funding, writing, and editing; CNS contributed to the formal analysis, visualisation, writing, and editing; BCH contributed to the data curation, methodology, writing, and editing; EH contributed to the data curation, methodology, writing, and editing; MBG contributed to the writing and editing; PML contributed to the investigation, writing, and editing; JLC contributed to the investigation, writing, and editing; DN contributed to the funding acquisition, investigation, writing, and editing; EB contributed to the data curation, investigation, writing, and editing; BM contributed to the data curation, methods, investigation, writing, and editing; CY contributed to the funding acquisition, investigation, writing, and editing; KM contributed to the data curation, investigation, writing, and editing; AJa contributed to the funding acquisition, investigation, writing, and editing; MC contributed to the investigation, writing, and editing; TS contributed to the investigation, writing, and editing; RR contributed to the investigation, writing, and editing; and AJi contributed to the investigation, writing, and editing.

Declaration of Interests

KNA reports consulting fees paid to her by the All of Us Research Study (US National Institutes of Health) and TrioHealth, and reports revenue from Coursera for an online course series. All other authors declare no competing interests.

Data sharing

Data held by the IeDEA consortium can be made available to other investigators, proposed use must be based on a concept note that is approved by the regional Steering Groups and the IeDEA Executive Committee.

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