INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

June 2019

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Studies' Updates

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
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INA-RESPOND newsletter

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FEATURES

INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, M. Ikhsan Jufri, Venty Muliana Sari

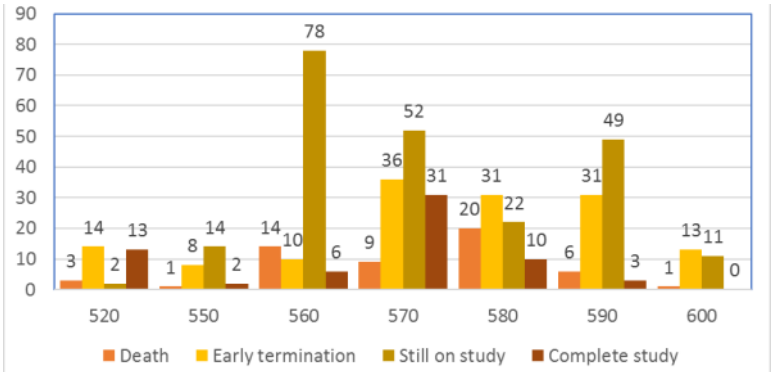

Figure 1.Participant status per site based on uploaded CRF per 31 May 2019

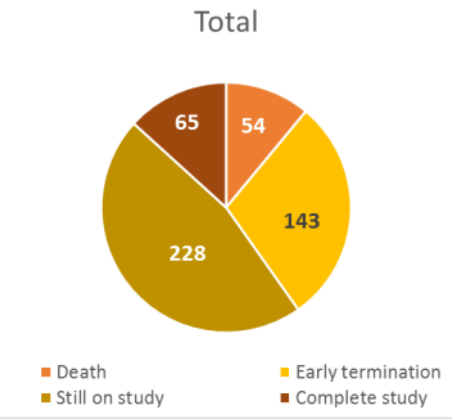

Figure 2. Total Participants Status based on uploaded CRF per 31 May 2019

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PARTICIPANT STATUS

Per 31 May 2019, the total ongoing participants in TRIPOD study are 228 out of 490 enrolled participants. Sixty-five participants have completed the study while 197 participants are terminated early (including death). Therefore, there are still 46,5% of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are 2 participants from site 520 (RS Sanglah Denpasar) who still need to be followed up, 14 participants from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 78 participants from site 560 (RSUP dr. Kariadi Semarang), 52 participants from site 570 (RSUD dr. Soetomo Surabaya), 22 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 49 participants from site 590 (RSUP Persahabatan Jakarta), and 11 participants from site 600 (RSUP dr. Adam Malik Medan).

Results for baseline culture and DST from all sites are ongoing. There are three sites have all the full result for culture and DST; site 520, site 550, and site 600. All culture and DST result will be on hold until further result information from the reference lab.

Site	Waiting for Baseline Study Culture Result	Waiting for Baseline DST Result
520 (n=32)	Complete	Complete
550 (n=25)	Complete	Complete
560 (n=108)	Complete	3
570 (n=128)	3	11
580 (n=83)	5	7
590 (n=89)	1	1
600 (n=25)	Complete	Complete

Figure 3.Culture and DST results up to 30 April 2019

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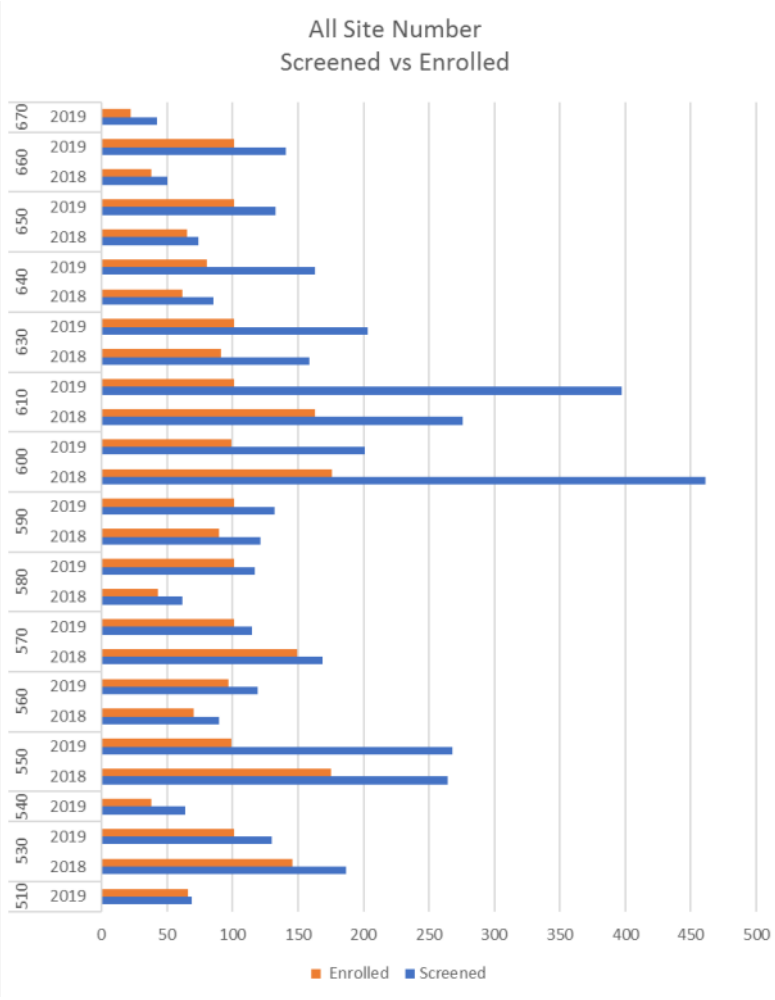
Since first activated on 10 January 2018, currently INA-PROACTIVE study has 15 active recruiting sites. By May 26, 2019, a total of 2,577 consisting of 116 pediatrics and 2,461 adults out of 4292 screened patients have been enrolled. The enrollment rate was 60.04% from total screening, details are shown in Figure 1 on the right.



The enrollment failure rate was 39.95% from total screening, details about reason for failures are shown in Figure 2 below.

*Reason for Enrollment Failure:

1. Suspect HIV
2. Refuse to consent or not cooperative
3. Unwilling to comply with study procedure
4. Plans to move away

A. No Show
B. Busy / in a hurry
C. Has been enrolled
D. Participated in other study
E. Hospitalized or unwell
F. Other: specify (e.g. no referral letter from other health facility, equipment trouble)

Several site visits for INA-PROACTIVE study has been conducted. The details are:

- Site Preparation Visit to RSUD Abepura, Papua on 13 – 15 May 2019
- Site Initiation Visit to RSUD Abepura, Papua on 21 – 22 May 2019
- Site Preparation Visit to RSUD Dr. TC Hillers, Maumere, NTT on 22 - 24 May 2019
- Site Initiation Visit to RSUD Dr. TC Hillers, Maumere, NTT on 28 – 29 May 2019
- Site Initiation Visit to RSUD Dr. Soedasrso, Pontianak on 28 – 29 May 2019

Site Number	Total Enrollment Failure	Reason for Enrollment Failure*									
		1	2	3	4	A	B	C	D	E	F
510	3	0	0	0	0	2	1	0	0	0	0
530	70	0	4	25	8	26	5	0	0	0	2
540	26	0	2	2	1	15	6	0	0	0	0
550	258	6	4	2	11	84	35	107	0	8	1
560	42	0	7	17	7	2	4	5	0	0	0
570	34	0	0	4	0	6	7	14	0	0	3
580	35	0	0	9	4	0	5	0	9	0	8
590	62	0	7	0	5	19	5	24	0	2	0
600	387	1	1	28	12	324	7	14	0	0	0
610	409	7	3	24	5	232	24	97	0	0	17
630	170	8	0	0	10	73	6	67	0	0	6
640	106	0	0	17	11	23	48	7	0	0	0
650	41	0	4	6	2	1	18	10	0	0	0
660	52	6	2	2	3	9	22	8	0	0	0
670	20	2	0	0	1	12	4	1	0	0	0

INA-RESPOND Newsletter

PREVENT US FROM MADNESS – LET US LIVE LONGER!

By: Aly Diana

Sad news, from January 1 to May 24, 2019, 940 individual cases of measles were confirmed in 26 states in the U.S.A. This is the highest number of cases reported in the U.S.A. since 1994 and since measles was declared eliminated in 2000. Measles is still prevalent in many parts of the world, so travelers with measles continue to bring the disease into the U.S.A. Therefore, measles spread when it reaches a community in the U.S.A, where groups of people are unvaccinated.

This phenomenon is not only can be observed in the U.S.A. According to WHO, there have been over 112,000 confirmed measles cases globally to date in 2019, an increase of 700% over the same period in 2018. Europe has also seen a 300% increase in measles infection. In 2018, 85% of children had received one dose of the two-dose MMR vaccine, while only 67% had received both.

Vaccine hesitancy, which is defined by WHO as a "delay in acceptance or refusal of vaccines despite the availability of vaccination services," has been reported in more than 90% of countries in the world. In many areas, immunization for measles, a vaccine-preventable disease that was largely eliminated following widespread use of the measles-mumps-rubella (MMR) vaccine, has decreased to less than the 95% threshold set by WHO as that required for herd immunity. WHO called vaccine hesitancy one of its top ten threats to global health in 2019.

WHO reports that vaccine-hesitant parents often find misinformation online. Therefore, engagement, listening, and information provided by medical professionals are often the best ways to address concerns. Pediatricians, family doctors, and other medical professionals have a key role in helping parents appreciate the benefits of vaccination. A sweet reminder that vaccination is one good example of primary prevention—which intervening a disease before health effects occur is important. Moreover, a clear presentation of the risks that delaying or refusing vaccination might pose to the child is pivotal to help parents understand how critical their decision is.

Efforts to eradicate a disease is enormous, let alone the cost involved. We cannot go back to the dark ages and accept the increased threat of measles. Removing vaccine exemptions for non-medical reasons has proven effective in the past in some countries. And while we must carefully balance the needs of public health with religious rights, vaccine hesitancy isn't just a personal issue. With a condition as contagious as measles, the choice not to vaccinate leaves the immunocompromised and children too young to be vaccinated at risk of infection. To regulate that unvaccinated child cannot be enrolled at nurseries or schools has proven to increase the proportion of vaccinated children, and probably should be promoted globally.

COMIC CORNER

Vaccine hesitancy is threatening the historical achievements made in reducing the burden of infectious diseases, which have plagued humanity for centuries. Only a collaborative effort between pediatricians, family doctors, parents, public health officials, governments, the technology sector, and civil society will allow myths and misinformation around vaccination to be dispelled. If we fail, the future health of unvaccinated children and their communities will suffer much. Could we afford it?

Notes: There were 3,995 confirmed measles cases in Indonesia in 2018, with a decrease in immunization coverage from 99.3% in 2012 to 89.8% in 2017.

References:

Pusat Data dan Informasi Kementerian Kesehatan RI. 2018. Situasi Campak dan Rubella di Indonesia. Jakarta, Indonesia.

CDC. 2019. Measles (Rubeola). https://www.cdc.gov/measles.html

World Health Organisation. Measles. https://www.who.int/immunization/diseases/measles/en/

Editorial. 2019. Measles eradication: a goal within reach, slipping away. Lancet; 393: 1669.

INA-RESPOND Newsletter

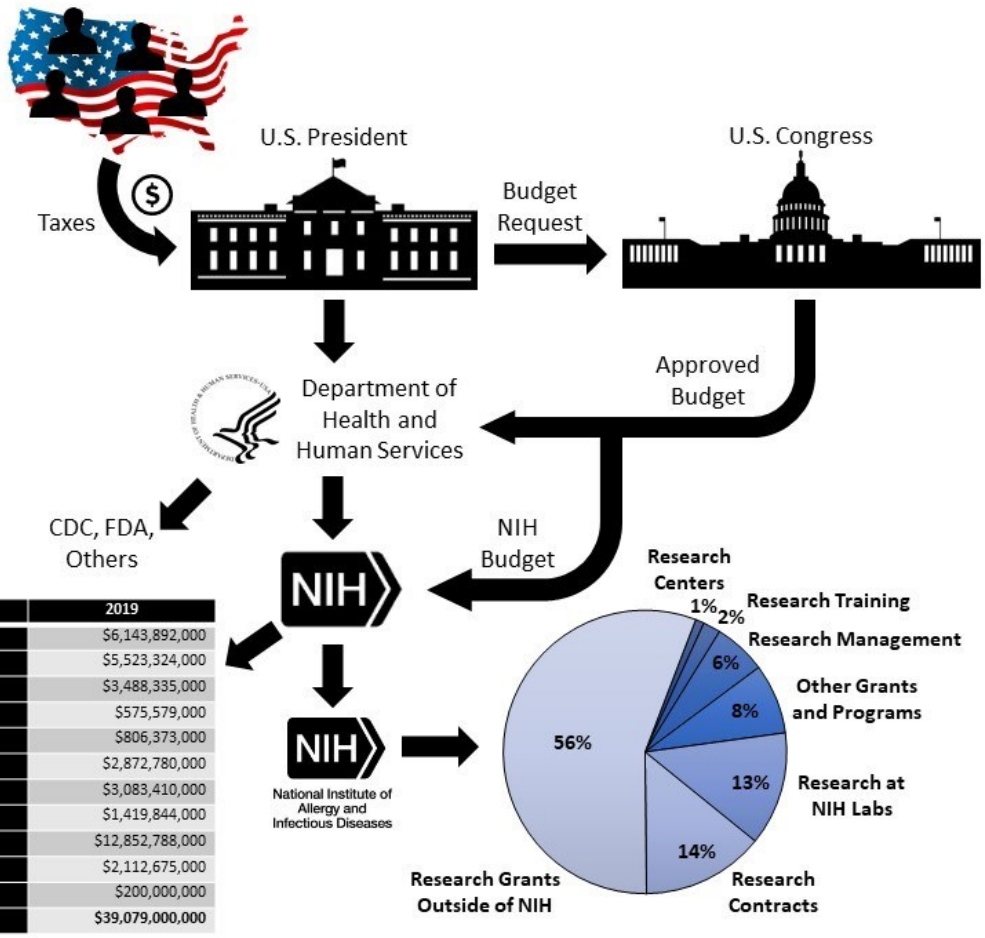
NIH FUNDING & GRANTS

By: Jacqueline Perodin, Ph.D., PMP; Aaron Neal, DPhil

The National Institutes of Health (NIH) is part of the United States (U.S.) Department of Health and Human Services which is responsible for medical research. Dr. Francis S. Collins heads the Office of the Director, which is responsible for setting policy for the NIH and planning/managing/coordinating programs and activities within. The NIH consists of 27 different Institutes and Centers (ICs), including the National Institute of Allergy and Infectious Diseases (NIAID), National Cancer Institute (NCI), National Heart, Lung and Blood Institute (NHLBI), and National Human Genome Research Institute (NHGRI), to name a few. A complete list of all NIH ICs is available at https://www.nih.gov/institutes-nih/list-nih-institutes-centers-offices.

NIH funding begins with U.S. taxpayers. Once a budget has been approved, NIH receives its funding from the U.S. Congress and, in turn, NIH ICs administrate their own budget per their specific research agenda. As funding is based on Americans' taxable income, transparency surrounding how funds generated using U.S. taxpayer monies is key. For this purpose, information on these government-created funds is available and accessible to the general public.

In fiscal year (FY) 2019, NIH's spending budget was approximately $39 billion U.S. dollars. These funds have been allocated across ICs as shown in the figure above, with NIAID's estimated operating budget of roughly $5.5 billion U.S. dollars (https://www.niaid.nih.gov/grants-contracts/niaid-budget-data-comparisons). Of note, the majority of NIH funds are spent outside of the NIH – for example, in FY2018, 83% of NIH's funding was dedicated to extramural research through a different mechanism such as research project grants, research training, research & development contracts, etc. (https://report.nih.gov/nihdatabook/report/283). Overall, the annual NIH budget supports various research and disease categories. Since the FY2015, approximately 280 different research and disease areas



Institute / Center	2019
NCI	$6,143,892,000
NIAID	$5,523,324,000
NHLBI	$3,488,335,000
NHGRI	$575,579,000
NCATS	$806,373,000
NIGMS	$2,872,780,000
NIA	$3,083,410,000
NIDA	$1,419,844,000
19 Other ICs	$12,852,788,000
OD	$2,112,675,000
B&F	$200,000,000
TOTAL	$39,079,000,000

have been financially supported by the NIH. The following table shows funding estimates across some research condition and disease areas for FY2019 – highlighted are some categories related to NIAID's research agenda.

For historical financial information, including a detailed list of research, conditions and disease areas funded, see https://report.nih.gov/categorical_spending.aspx.

In support of global health research on infectious diseases, the Collaborative Clinical Research Branch (CCRB) of NIAID's Division of Clinical Research (DCR) uses their allotted funds to address both sustainable research capacity and emergency responses around the world. Annually allotted funds, as shown for FY2019 in the above table, are used by NIAID DCR/CCRB to support the development of sustainable research capacity domestically and internationally through clinical research networks and researchers. In addition to INA-RESPOND, CCRB supports the following partners:

- Infectious Disease Clinical Research Program (http://www.idcrp.org/)
- CCRB Laboratories (https://www.niaid.nih.gov/about/ccrb-laboratories)
- Mali-University Clinical Research Center (https://www.niaid.nih.gov/research/mali-university-clinical-research-center)
- Mexican Emerging Infectious Disease Clinical Research Network (https://www.redmexei.mx/portal/)
- Partnership of Clinical Research in Guinea (https://www.niaid.nih.gov/research/partnership-clinical-research-guinea)

Through these partnerships, CCRB works with these collaborators to build-up expertise and provide the necessary resources and abilities to compete for funding grants. Using additional funds, NIAID DCR/CCRB has also been responsible for launching the U.S.'s emergency research response to address infectious disease outbreaks. In the event Congress authorizes extra funding in response to an emergency (e.g., Ebola in West Africa, Zika in the Americas), the Division uses these funds to issue new basic science grants/contracts, accelerate vaccine development, and develop research capacity in epidemic hotspots.

Research/Disease Categories	2019
Alzheimer's Disease	$2,305,000,000
Antimicrobial Resistance	$566,000,000
Autoimmune Disease	$965,000,000
Brain Cancer	$375,000,000
Brain Disorders	$6,448,000,000
Breast Cancer	$743,000,000
Cancer Genomics	$1,086,000,000
Cardiovascular	$2,348,000,000
Cerebrovascular	$745,000,000
Clinical Research	$15,023,000,000
Dementia	$2,007,000,000
Emerging Infectious Diseases	$2,915,000,000
Genetics	$9,551,000,000
Heart Disease	$1,452,000,000
HIV / AIDS	$3,045,000,000
Human Genome	$3,821,000,000
Immunization	$2,330,000,000
Infectious Diseases	$6,317,000,000
Kidney Disease	$619,000,000
Liver Disease	$841,000,000
Lung	$1,935,000,000
Mental Health	$3,232,000,000
Multiple Sclerosis	$117,000,000
Neurosciences	$8,945,000,000
Osteoporosis	$157,000,000
Ovarian Cancer	$163,000,000
Pancreatic Cancer	$221,000,000
Parkinson's Disease	$201,000,000
Pneumonia & Influenza	$523,000,000
Prevention	$9,322,000,000
Prostate Cancer	$271,000,000
Rare Diseases	$5,459,000,000
Sepsis	$140,000,000
Tobacco	$314,000,000
Tuberculosis	$422,000,000
Women's Health	$5,426,000,000

Jacqueline Perodin, Ph.D. —
Clinical Project Manager III
Clinical Monitoring Research Program Directorate (CMRPD)
Frederick National Laboratory for Cancer Research (FNLCR)

NIH's Fogarty International Center supports global health research by sustaining basic, clinical, and applied research and training for the U.S. and foreign investigators (https://www.fic.nih.gov/Pages/Default.aspx). This Center - led by Dr. Roger I. Glass, Director of the Fogarty International Center and Associate Director for International Research - builds partnerships between health research institutions in the U.S. and foreign countries and trains scientists to address global health needs. Their vision is "a world in which the frontiers of health research extend across the globe and advances in science are implemented to reduce the burden of disease, promote health, and extend longevity for all people." The Fogarty International Center has research training programs under which they offer funding opportunities. These grants are provided to low- and middle-income countries in various program areas to build sustainable research capacity, such as the following current opportunities: HIV Research Training, Global Infectious Disease Research Training, Bioinformatics Research Training (H3Africa), and Chronic Noncommunicable Diseases and Disorders Research Training. Worldwide, approximately 6,000 scientists have received research training through Fogarty programs. Information on available program funding opportunities, eligibility, how to apply, and more can be found on the Fogarty International Center's website (https://www.fic.nih.gov/Pages/Default.aspx).

INA-RESPOND Newsletter

SCIENCE CORNER

HIV AND AGING

By: dr. Herman Kosasih

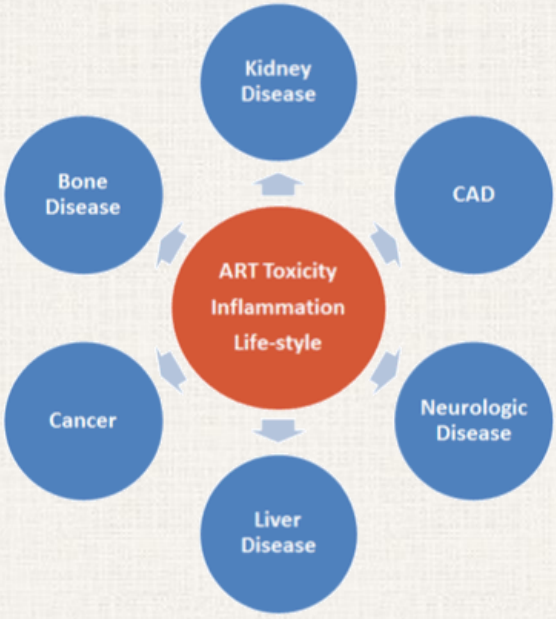
Source :https://www.hivplusmag.com/treatment/2019/4/16/aging-gracefully-hiv-just-became-much-easier

Before the effective anti-retroviral therapy (ART), most patients living with HIV (PLWH) usually died not long after the diagnosis as they often came with life-threatening opportunistic infections. So many of them were young and bright. Thanks to the ART, HIV is now considered as a manageable chronic disease, and now PLWHs have almost the same life expectancy as the general population's.

By 2030, up to 70% of PLWH will be over the age of 50. In Indonesia as the proportion of newly identified cases in the age groups of 25 to 49 years and ≥50 years of age in the last ten years is around 80%, we will also see a similar trend.

However, the 'success' of ART comes at the price of 'unexpected' consequences. Several research findings show that many diseases that are usually found in HIV-negative people during their older age (60s-70s) occur in younger age in PLWH. On the contrary, a large study among US military veterans that compare people of similar ages with similar life experience, found age-associated events (myocardial infarct, renal disease, non-AIDS defining cancer) occurred at similar ages in both PLWH and HIV-negative adults, assuring PLWHs that they are unlikely to experience these conditions decades earlier than those aging without HIV. Also, research findings of HIV and aging must be carefully interpreted as they can often be misleading. For example, the finding that the comparison between the mean age of PLWH and HIV-negative people being diagnosed with type 2 diabetes is 47 to 54 is not necessarily evidence of premature aging, but may simply be because there are not many PLWH in the older age groups, PLWHs tend to visit their clinicians more often than the general population (leading to early diagnosis), or the demography and lifestyle in the two groups are different.

Although the concept of premature aging is still debatable, there is no doubt that PLWH has a higher risk of age-associated events such as cardiovascular diseases, liver and kidney diseases, cognitive dysfunction, osteoporosis, and Non-AIDS malignancies, switching the cause of mortality from AIDS-related diseases to non-AIDS-related events.



Factors contributing to age-related illnesses can be grouped into inflammation, lifestyle and ART toxicity. Experts also agree that all factors probably combine to have an impact.

Although taking HIV treatment suppresses HIV viruses to an undetectable level, this does not mean that replication is blocked entirely. The constant low -level replication of the virus keeps the immune system chronically in high alert, causing ongoing low-level inflammation and immune activation. Infections with other viruses, lifestyle (smoking, heavy drinking, drug use, high-fat diets) may also contribute to this condition. During this condition, researchers found high level of cytokines or biomarkers such as interleukin-6, CRP, CD14, CD163, and D-Dimer may be associated with a wide range of health problems shown in the figure above.

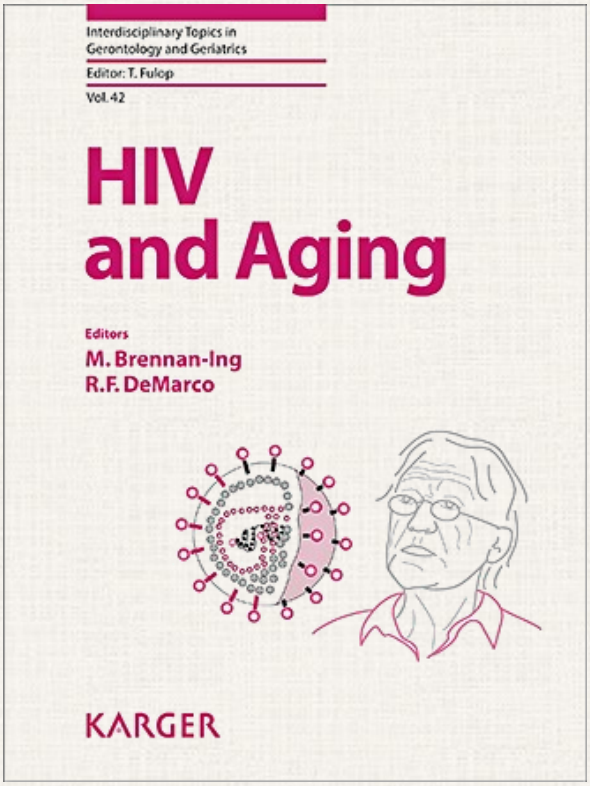
The role of specific ART regimens and the increased risk of age-associated dysfunction is still unclear as some studies reporting increased risk with protease inhibitors, NRTI, Efavirenz, and D-drug, whereas others not. Some older drugs such as stavudine and didanosine are rarely used nowadays as modern anti-HIV drugs are much safer and less likely to contribute to age-related conditions in PLWH.

To slow the aging process and prevent the age-related illness from occurring, PLWH can be advised to do quite a lot of things, such as:

- keep the viral load undetectable by adhering the ART,
- monitor health status regularly so that any problems can be detected early,
- take preventive medicine such as statin or blood pressure medication,
- have a better lifestyle (stop smoking, reduce alcohol),
- eat healthy food,
- maintain a healthy weight,
- exercise regularly,
- keep the brain active by doing activities that stimulate the mind
- stay in contact with friends, family, club, or organization.

Further reading:

Falutz, J, et al2012. Aging gracefully with HIV: is it possible?, ACCM
AIDSMAP 2017. Factsheet HIV and the ageing process.
Rajasuriar, et al. 2018. Integrative biomarkers of biologic aging in HIV
McGettrick, P et al. 2018. Ageing with HIV.



Pic from HIV and Aging (M Brennan-Ing, R.F.De Marco, Karger)
https://vitalrecord.tamhsc.edu/10-common-elderly-health-issues/

INA-RESPOND Newsletter

MONITORING CHILDREN'S SCREEN TIME

By: dr. Marco Ariono

Nowadays, most people have become well-adjusted to using digitals tools, such as smartphone, computer, or internet. Exposure to digital media is increasing, and screen time affects children and family. Screen time refer to time spent with any screen, including smartphones, tablets, television, video games, computers or wearable technology.[1,2]

For the Z Generation, the 'digital natives' who have grown up surrounded by digital information and entertainment on screens, screen time is a significant part of their contemporary life. American Academy of Pediatrics (AAP) recommends parents limit their children's daily screen time, with specific time limits for preschool children and a general suggestion of limiting time on screens for older children and adolescents. Recently World Health Organization has decided to include gaming disorder in the 11th revision of the International Classification of Diseases.[3,4]

There is evidence that screen time is associated with obesity, harmful effects on irritability, low mood and cognitive and socioemotional development, leading to poor educational performance.[3]

Screen Time Current Trend

In 2011, a study estimated that 1 in 5 people are physically inactive. Individuals engaging in light, moderate or vigorous physical activity had a significantly lower risk for cardiovascular disease mortality. In Canada, the prevalence of obesity was significantly higher in people who watched television for more than 21 hours per week and lower in people who watched TV for fewer than 5 hours per week.[5]

There are some possible mechanisms to explain the effects of screen media exposure on obesity. These include displacing physical activity, increasing energy intake from eating while viewing and the effects of advertising, and reducing sleep. The increased access to new digital media (e.g., smartphones and tablets) devices has contributed to a rapid rise in average screen time exposure for children. Total daily screen time across devices in children 8 to 18 years old has risen from five to approximately eight hours since 1999, far exceeding the AAP recommendation of two hours or less. [6,7]

The development of technology has led to electronic media becoming an integral part of life. Exposure to screens tends to start from very early infancy. Children spend a substantial proportion of their daily waking hours on screen-based activities, about 8 hours in many cases. Parents believe that media content is educational. One survey found that 29% of the 1000 parents interviewed allowed their children younger than two years old to watch television because it is 'good for their brains.' One study of mothers confirmed that TV viewing by their children was useful in accomplishing household tasks. Another study found that parents usually utilized mobile media to occupy their children when eating out.[8,9]

Health impact

Currently, 90% of parents report that their children younger than two years watch some form of electronic media. But, young children have difficulty discriminating between events on a video and the same information presented by a live person, which is referred to as "video deficit." Children 12 to 18 months of age are more likely to learn from a live presentation than from a screen one and are also more likely to remember the information from a live presentation afterward. Early learning is easier, more enriching and developmentally more efficient when experienced live, interactively, in real time and space, and with real people. Screen media exposure is one of the best-documented causes of obesity in children and, likewise, obesity is one of the best-documented outcomes of screen media exposure. These include displacing physical activity, increasing energy intake from eating while viewing and the effects of advertising, and reducing sleep. [1,6,8]

There are established individual associations between youth screen time and compromised sleep duration and quality. Higher levels of screen time cause sleep disturbances have been attributed to environmental, psychosocial, and biological causes. Screen-based activities often delay bedtime or truncate total sleep time. One psychosocial source may be arousal due to the content of the media, interfering with the ability to fall and stay asleep. A potential biological mechanism is the effect of screen light on both circadian rhythm and alertness.[7,10]

Screen time alters behavior and thus leads to negative outcomes. Watching screens can distract children from feeling full, and this may be contributing to the increased energy intake. Also, children are often exposed to advertising while using screens, which appears to lead to a higher intake of unhealthy foods. Screen use exposes children and young people to harmful content, through cyberbullying, watching violence or pornography, and unrealistic imagery.[11]

Recommendations

AAP recommendations:[12,13]

- 0-18 months: avoid the use of screen media other than video-chatting. Parents of children 18 to 24 months of age

who want to introduce digital media should choose high-quality programming, and watch it with their children to help them understand what they're seeing.

- Two to five years: limit screen use to 1 hour per day of high-quality programs. Parents should co-view media with children to help them understand what they are seeing and apply it to the world around them.
- Six years and older: place consistent limits on the time spent using media, and the types of media, and make sure media does not take the place of adequate sleep, physical activity and other behaviors essential to health.

Strategy[1,14]

Minimize screen time:

- Screen time for children younger than two years is not recommended.
- For children 2 to 5 years, limit routine or regular screen time to less than 1 hour per day.
- Ensure that sedentary screen time is not a routine part of child care for children younger than five years.
- Minimize parents' screen use when young children are present, especially during mealtimes, play, and other prime opportunities for social learning.
- Prioritize interactions with children through conversation, play, and healthy/active routines.
- Minimizing screen time leaves more time for face-to-face interactions, which is how young children learn best.
- Maintain daily 'screen-free' times, especially for family meals and book-sharing.
- Avoid screens for at least 1 hour before bedtime, given the potential for melatonin-suppressing effects.

Mitigate (reduce) the risks associated with screen time:

- Combine touch screen use with creative or active play.
- Watch with children. Adults can connect what is being viewed with real life, and build language and cognitive skills, such as attention, memory, and thinking.
- Be present and engaged when screens are used and, whenever possible, co-view with children.
- Be aware of the content and prioritize educational, age-appropriate, and interactive programming.
- Actively curate children's screen activities by prioritizing educational content or apps, avoiding mainstream or commercial programs
- Choose when to use media together, and turn off screens when they are not in use.
- Use parenting strategies that teach self-regulation, calming and limit-setting.

Adults should model healthy screen use:

- Choose healthy alternatives, such as reading, outdoor play and creative, hands-on activities.
- Turn off their devices at home during family time.
- Turn off screens when not in use and avoid background TV.

Reference

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