INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

April 2020

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

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TRIPOD & INA-PROACTIVE Study Updates

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

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PARTICIPANT STATUS

Per 04 April 2020, the total ongoing participants in the TRIPOD study are 58 out of 490 enrolled participants. From those 58 ongoing participants, 36 are still on TB treatment while 22 are waiting for a 6-month post-treatment visit. Two hundred and two participants have completed the study, while 230 participants are terminated early (including death). Therefore, there are still 11.9% of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are 1 participant from site 520 (RS Sanglah Denpasar) who still need to be followed up, 2 participants from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 23 participants from site 560 (RSUP dr. Kariadi Semarang), 6 participants from site 570 (RSUD dr. Soetomo Surabaya), 9 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 16 participants from site 590 (RSUP Persahabatan Jakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

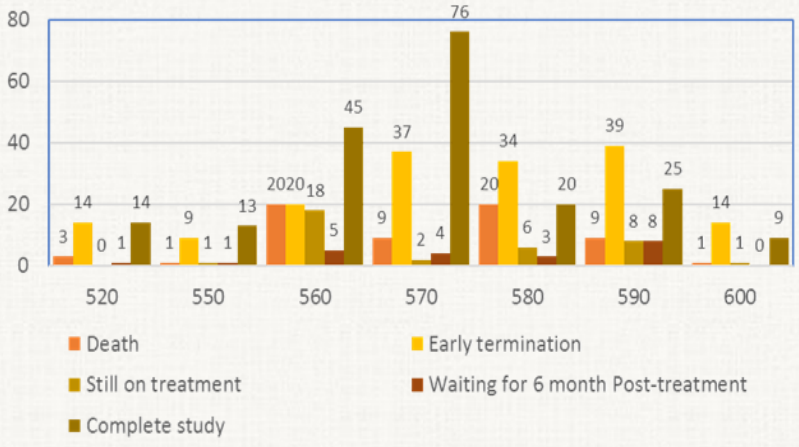

Figure 1.Participant status per site based on uploaded CRF per 4 Apr 2020

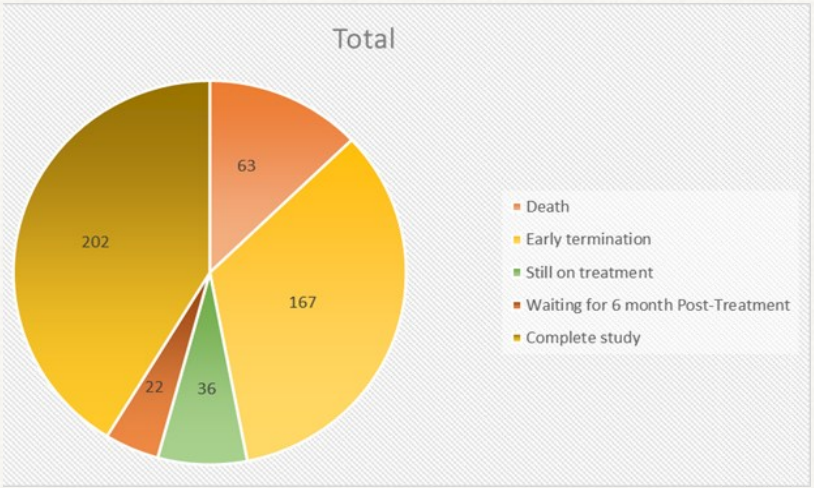

Figure 2. Total Participants Status based on uploaded CRF per 4 Apr 2020

MTA SUBMISSION

For the TRIPOD study, we plan to send some samples abroad to do some confirmatory assessments. Some of the collected isolates have been calculated and ready to be sent once MTA approved. Confirmatory assessments that will be conducted are DST-Testing and Pyrazinamide. Those testing will be performed in the National Jewish Lab, Colorado.

WORK FROM HOME DURING COVID-19 PANDEMIC

Since 18 March 2020, Secretariat enacted work from home during the Covid-19 pandemic. All activities have been adjusted due to the situation. One of the adjustments is to halt all follow up in the TRIPOD study until further notice. Some hospitals also have their own regulatory for TB patients during a pandemic. However, not all sites do total work from home. Some Research Assistants come to sites only once a week, while others still have to be present at work. To respond to these differences, the TRIPOD study team creates activities to maintain productivity during the work-from-home period, such as portal management, remote monitoring, more teleconferences, and virtual meetings.

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As a response in connection with the COVID-19 pandemic and the Decree of the Minister of Health of the Republic of Indonesia number HK.01.07/Menkes/169/2020 regarding The Appointment of Certain Reference Hospital for the Prevention of Emerging Infection Diseases, where hospitals are expected to concentrate on providing services for COVID-19 patients; INA-RESPOND Chairman has decided for all INA-RESPOND Research Sites to temporarily suspend the recruitment of subjects and follow-up visits, starting from 16 March 2020 until further notice. The notification has been informed to the Steering Committee members, PIs, Co-PIs, and all site team. INA-RESPOND secretariat has also submitted a memo to the ethical committees regarding this decision.

Due to the enrollment halt, the latest update of the total screened and enrolled subjects from 19 PROACTIVE study sites per 15 March 2020 is as seen in the table below. When the enrollment is resumed, the three last activated sites will continue to recruit new subjects that scheduled until 30 June 2020. They are Site 700 (T.C. Hillers Hospital in Maumere), Site 690 (Abepura Hospital in Papua), and Site 520 (Sanglah Hospital in Bali).

During the enrolment and follow-up halt, the site teams are expected to focus on working for completing the previously pending data, in addition to conducting refresher training related to the study procedure, update the study documents, discuss the cause of death for the unknown or doubtful death cases, discuss the trouble-shooting of some specimen processing problems and other site-specific discussions.

Moreover, regarding the follow-up visit, there is an exception for subjects with scheduled visits that are nearing the end of the window period in the temporary stopping period, the follow-up visit can be carried out to minimize missed visits due to the absence of the subject. Therefore, retention of the subject can be maintained well.

No	Site# / Name	1st Enrollment	Enrollment stop	# Screened			# Enrolled			Active Participants
				Ped	Adult	Total	Ped	Adult	Total	
1	510 – Hasan Sadikin	7-Feb-19	31-Dec-19	12	226	238	10	198	208	208
2	520 – Sanglah*	7-Nov-19	30 Jun 20	7	168	175	4	97	101	100
3	530 – Cipto M.	3-May-18	31-Aug-19	38	365	403	36	274	310	301
4	540 – Sulianti Saroso	25-Feb-19	31-Dec-19	26	225	251	20	162	182	182
5	550 – Wahidin	14-Mar-18	31-Aug-19	17	695	712	10	327	337	322
6	560 – Kariadi	14-Aug-18	31-Aug-19	21	285	306	12	218	230	222
7	570 – Soetomo	26-Apr-18	31-Aug-19	7	365	372	6	307	313	304
8	580 – Sardjito	14-Sep-18	30-Sep-19	5	290	295	4	216	220	219
9	590 – Persahabatan	19-Jul-18	31-Aug-19	12	324	336	10	239	249	229
10	600 – Adam Malik	12-Mar-18	31-Aug-19	17	778	795	2	336	338	324
11	610 – Tangerang	10-Jan-18	31-Aug-19	60	890	950	17	310	327	312
12	630 – Ansari Saleh	17-Jul-18	31-Aug-19	19	447	466	9	236	245	243
13	640 – St. Carolus	13-Aug-18	30-Sep-19	0	380	380	0	225	225	225
14	650 – Budi Kemuliaan	2-Aug-18	31-Aug-19	4	306	310	4	225	229	222
15	660 – AW Sjahranie	3-Oct-18	30-Sep-19	25	292	317	17	205	222	220
16	670 – Zainoel Abidin	9-Apr-19	31-Dec-19	17	384	401	5	121	126	123
17	680 – Soedarso	4-Jul-19	31-Dec-19	8	139	147	8	107	115	115
18	690 – Abepura*	2-Jul-19	30-Jun-20	7	200	207	4	132	136	134
19	700 – TC Hilers*	8-Jul-19	30-Jun-20	10	207	217	7	157	164	162
Total				**312**	**6966**	**7278**	**185**	**4092**	**4277**	**4167**

Table 1. Total Screened vs. Enrolled in All Sites

INA-RESPOND Newsletter

Site 680: RSUD Soedarso, Pontianak

By: dr. Ellissa and dr. Irfan Muhammad Alqadrie

Left to right : Ms. Herlina, dr. Ellissa, dr. Wiwi, dr. Ivan Sp.PD, dr. Justina Sp.PK, Ms. Emy, dr. Irfan

Pontianak is a city famous for "Kuntilanak" and its equator. This capital city of West Kalimantan is renowned for its culinary variety that is suitable for culinary lovers, like choi pan, bubur paddas, pacri nanas, durian, etc. RSUD Soedarso, which is one of the INA-RESPOND sites, is a reference hospital in Pontianak, West Kalimantan. Since it is a reference hospital, it has research subjects coming from several districts and cities.

Since this is RSUD Soedarso's first experience participating in research with INA-RESPOND, there are many things we must learn. With the help of the network's Site Specialists, DM team, and Monitoring team, we were greatly assisted and supported in the adjustment process. We thank Mr. Ikhsan, Ms. Vera, Mr. Kris, and dr. Henny.

Principal Investigator (PI)

Name : dr. Ivan Lumban Toruan Sp.PD KHOM
Birth Place and Birth Date : Palembang, 22 March 1970
Formal Education : FK Universitas Sriwijaya (S1 and Specialist) Universitas Padjajaran (Subspecialist)

PI from site 680 is dr. Ivan Lumban Toruan Sp.PD KHOM. Born on 22 March 1970, dr. Ivan Lumban Toruan has just finished his Hemato Oncology Subspecialist study at Padjadjaran University. This internal medicine specialist who has been serving at RSUD Soedarso since 2010 previously came to West Kalimantan in 1996. Research Assistants often go to him at the internal medicine polyclinic to give him the teleconference and study results as well as any issues related to the study that came up

Co-PI

Name : dr. Muchamad Budi Nugroho Sp.A, M. Kes.
Birth Place and Birth Date : Solo, 2 May 1970
Formal Education : Faculty of Medicine, Sebelas Maret University (Undergraduate) Universitas Gadjah Mada (Specialist and Master in Clinical Medicine)

dr. Ivan Lumban Toruan Sp.PD KHOM

dr. Muchamad Budi Nugroho Sp.A, M. Kes.

We have three Co-Pis. One of the co-PIs from site 680 is dr. Muchamad Budi Nugroho Sp.A, M.Kes. We usually call him dr. Budi. He has many tricks and a voice that can calm crying children. Dr. Budi was born in Solo, 2 May, 50 years ago. Before continuing his study, he served in several remote areas in West Kalimantan, from the Public Health Center in Sintang to the one in Melawi. Also, before he became a doctor at RSUD Soedarso, he worked at RSUD Abdul Aziz Singkawang from 2008-2013.

Name : dr. Justina Maria Eka Diana Juswarini Sp.PK
Birth Place/ Birth Date : Mojokerto, 28 December 1955
Formal Education : Faculty of Medicine, Brawijaya University (Undergraduate) Airlangga University (Specialist)

Another co-PI from site 680 is dr. Justina Maria Eka Diana Juswarini Sp.PK. We usually call her by "dr. Yus or Bu Yus". She was born in Mojokerto 65 years ago. Her calm and gentle speaking style makes the RAs love to hang in the laboratory. Dr. Justina has been the Head of the Laboratory at RSUD Soedarso since 1997. Previously, she served at Rasau Jaya Public Health Center, which is now a part of Kubu Raya district, West Kalimantan. She was accommodating in the moving process of the INA-RESPOND laboratory at the site to a new and much more beautiful building. Thank you very much, dr. Jus.

Name : dr. Wiwi Endang S.
Birth Place/ Birth Date : Nanga Pinoh, 10 April 1979
Formal Education : Faculty of Medicine, Muhammadiyah University of Yogyakarta (Undergraduate)

The third Co-PI is dr. Wiwi Endang S. We usually call her "Bu Wi" or "dr. Wiwi". She was born in Nanga Pinoh and has been in the HIV world for more than a decade. She has participated in a lot of HIV training and has been a counselor since 2004. Bu Wi has a young soul, and she loves bringing her cooking to work so that everyone can eat together. In addition to cooking, she likes sewing.

Research Assistants (RAs)

Name : dr. Ellissa
Birth Place/ Birth Date : Jakarta, 08 October 1993
Formal Education : Faculty of Medicine, Tarumanagara University (Undergraduate)

The first RA from Site 680 is dr. Ellissa. Everybody calls her "El," but she doesn't have any brother called Al or Dul. Previously, dr. Ellissa served in Karangasem, Bali before

she was relocated. El is passionate about learning, from being technologically illiterate to a person who is good at operating sophisticated technological products.

Name : dr. Irfan Muhammad Alqadrie
Birth Place/ Birth Date : Pontianak, 03 August 1994
Formal Education : Faculty of Medicine, Islamic University of Indonesia (Undergraduate)

The second RA is dr. Irfan Muhammad Alqadrie. His colleagues usually call him "Irfan" or "Ipan." Dr. Irfan served in RSUD and PHC in Melawi before he returned to his hometown. Irfan is known for his relaxed nature, and he is also a fast learner. His many interests took him to several competitions like constitution-memorizing and religious preaching competitions.

Lab Technicians (LT)

Name : Herlina
Birth Place/ Birth Date : Pontianak, 25 January 1977
Formal Education : Poltekkes Kemenkes (D3)

Our first LT is Herlina. We usually call her "Kak Lina." Her calm nature makes the subjects at ease when their blood is drawn. She has attended training at the Ministry of Health to become a facilitator in the field of HIV, HBsAg, and Syphilis. Research Assistants go to her every month to see if there is anything she wants to resupply.

Name : Sudaryanto
Birth Place/ Birth Date : Pontianak, 11 January 1975
Formal Education : Health Analyst Academy

The next LT is Sudaryanto. We usually call him Pak Yanto. He is outgoing and fun; he loves telling jokes or funny stories to make subjects relaxed and unafraid when he wants to take their blood. He has also attended training by the Ministry of Health on Avian Influenza and Biosafety and Biosecurity. By the way, during the moving process, he was really helpful.

Nurse

Name : Emy Suyanti AMK, SKM
Birth Place and Birth Date : Pontianak, 30 May 1977
Formal Education : Muhammadiyah University of Pontianak (Undergraduate)

Our VCT polyclinic nurse is Emy Suyanti AMK, SKM, whom we usually call "Kak Emy." She has worked at RSUD Soedarso since 1996. She nearly remembers all of the research subjects. She helps the Research Assistants in contacting the study participants. Enrollments and follow-ups wouldn't have been smooth without her.

INA-RESPOND Newsletter

PARTICIPATION OF INA RESPOND IN ADAPTIVE COVID-19 TREATMENT TRIAL (ACTT) AND SOLIDARITY TRIAL

By: Yan Mardian

SCIENCE CORNER

Participation of INA RESPOND in Adaptive COVID-19 Treatment Trial (ACTT) by National Institute of Allergy and Infectious Diseases (NIAID) and SOLIDARITY trial by the World Health Organization (WHO)

The epidemic of novel coronavirus (COVID-19) infections that began in China in late 2019 has rapidly grown, and cases have been reported worldwide. Until now, there are no drugs proven to be effective against COVID-19, despite its continuous widespread transmission and deaths reported throughout the globe.

To address that issue, WHO, on 20 March, announced the launch of SOLIDARITY, an unprecedented, large randomized trial, coordinated push to collect robust scientific data rapidly during a pandemic. The study, which will enroll many thousands of patients in dozens of countries, has emphasized simplicity so that even hospitals overwhelmed by an onslaught of COVID-19 patients can participate. Rather than taking years to develop and test compounds from scratch, WHO expert groups advised the four repurposed drugs that are already approved for other diseases and have acceptable safety profiles. They're also looking at experimental medicines that have performed well in animal studies against the other two deadly coronaviruses, the Severe Acute Respiratory Syndrome (SARS) and the Middle East respiratory syndrome (MERS) coronavirus. For the SOLIDARITY study, WHO chose an experimental antiviral called remdesivir; the malaria medication chloroquine (or its chemical cousin hydroxychloroquine); a combination of the HIV drugs lopinavir and ritonavir; and that combination plus interferon-beta, an immune system messenger that can help cripple viruses. The treatments would stop the virus by different mechanisms, but each has drawbacks.

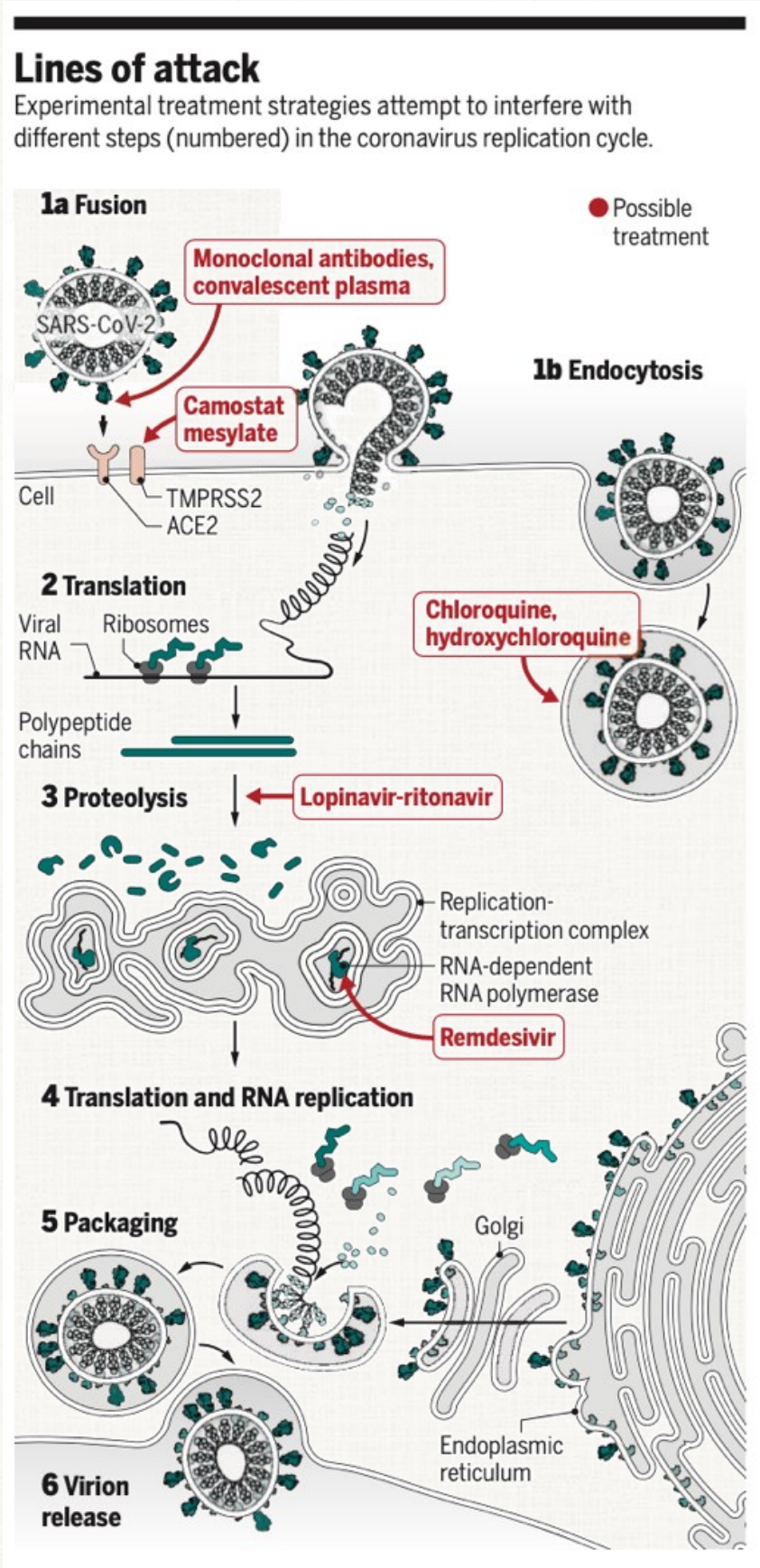
The aim of the SOLIDARITY trial is to compare the effects on major outcomes in the hospital of the local standard of care alone versus the local standard of care plus one of four alternative antiviral agents. Adults (age ≥18 years) recently hospital-

ized, or already in the hospital, with definite COVID and, in the view of the responsible doctor, no contra-indication to any of the study drugs will be randomly allocated between these five arms,

- Local standard of care alone, OR local standard of care plus one of
- Remdesivir (daily infusion for ten days)
- Chloroquine or hydroxychloroquine (two oral loading doses, then orally twice daily for ten days)
- Lopinavir with Ritonavir (orally twice daily for 14 days)
- Lopinavir with Ritonavir (ditto) plus Interferon (daily injection for six days).

The primary objective of this large international randomized trial is to provide reliable estimates on any effects of these antiviral treatments on in-hospital mortality in moderate and severe COVID. While The secondary objectives are to assess any effects of these antiviral treatments on hospital duration and receipt of ventilation or intensive care and to identify any serious adverse reactions.

In parallel with WHO Solidarity study, the National Institute of Allergy and Infectious Diseases (NIAID) is currently conducting a randomized, double-blind, placebo-controlled trial. This study is a multicenter trial that will be held in up to approximately 75 sites globally to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19, called Adaptive COVID-19 Treatment Trial (ACTT). The study is double-blind, meaning trial investigators and participants would not know who is receiving remdesivir or placebo. Participants in the investigational treatment group will receive 200 milligrams (mg) of remdesivir intravenously on the first day of enrollment to the study. They will receive another 100 mg each day for the duration of hospitalization for up to 10 days total. The placebo group will receive, at an equal volume, a solution that resembles remdesivir but contains only inactive ingredients. Subjects will be assessed every day while hospitalized. Discharged subjects will be asked to attend study visits at Days 15 and 29. All subjects will undergo a series of efficacy, safety, and laboratory assessments. The primary objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adults hospitalized with COVID-19.



Remdesivir (GS-5374) is a prodrug that was first developed by Gilead Sciences to combat Ebola and related viruses (filoviruses, paramyxoviruses, and coronaviruses). The antiviral works by interfering viral replication through inhibition of the RNA-dependent RNA polymerase enzyme. As a fun fact, this drug proved insignificant in helping patients in the Democratic Republic of Congo in the Ebola outbreak in 2019. However, in 2017, researchers showed promising effects of remdesivir against SARS and MERS by in vitro and in vivo studies, despite the presence of exoribonuclease, a proofing capacity of coronavirus, which decrease the mutation of that coronavirus. Due to promising results on basic study, the researchers suspect Remdesivir can also be used in COVID-19 patients. The use of this drug, which is given intravenously, has been used in hundreds of COVID-19 patients in the United States and Europe, and some doctors have reported the benefits of giving this drug, although nothing has been conclusive yet. Its side effects are usually not frequent or severe and last only a few days. These involve digestive discomfort (such as loss of appetite, heartburn, feeling sick or being sick, loose stool or constipation) or general discomfort (such as trembling, itching, headache, dizziness, or unusual feelings in the ear). There are some reports that some patients' blood tests show changes in kidney or liver function, but these are reversible when the drug is stopped.

Lopinavir was initially used as one of human immunodeficiency virus (HIV) drug, in specific as aspartate protease inhibitors that inhibit HIV life cycle. While Ritonavir, combined with Lopinavir, can increase the half-life of Lopinavir in plasma through inhibition of cytochrome P450. Some recent studies have shown the promising effect of Lopinavir/Ritonavir for its inhibitory activity against SARS-CoV in vitro. Allegedly, this inhibitory effect was observed by its effects on Mpro, the main enzyme for coronavirus replication. Several reports also have addressed Lopinavir/Ritonavir inhibitory activity against MERS-CoV, both in vitro and in vivo. Besides, there are several MERS case reports had shown a combination of Lopinavir-ritonavir with ribavirin and interferon alpha can accelerate viral clearance and increase patient survival in these cases. However, the efficacy and safety testing for the use of Lopinavir and Ritonavir in COVID-19 cases is still minimal.

A study conducted in China on the administration of Lopinavir-Ritonavir (400/100 mg twice daily for 14 days) in 199 adults COVID-19 patients (99 receiving Lopinavir-ritonavir, and 100 receiving standard medical care) showed unfavorable results. In a study published in NEJM last month, the percentage of viral RNA positivity between the treatment group and the control group was not significantly different. However, there is a tendency of a bit shorter hospitalization period in the treatment group. The article also highlighted some gastrointestinal side effects such as nausea, vomiting, and diarrhea were more common in the treatment group, with four cases being quite severe (acute gastritis and skin eruption). Some other studies also showed several other side effects related to Liponavir/Ritonavir administration, such as increased liver enzymes, blurred vision, and asymptomatic bradycardia.

Interferon is made by Merck Sharp and Dohme company and generally used to treat patients with multiple sclerosis, with quite an excellent safety profile. A study in MERS-CoV showed that coronavirus could weaken the interferon response (IFN) of the innate immune system, and inhibit adaptive immune responses, specifically T-helper-1 (Th-1) cells. Supported by this theoretical basis, several in vitro studies have shown that IFN-α and IFN-β have inhibitory effects on MERS-CoV and SARS-CoV. One in vivo study showed that common marmosets infected with MERS-CoV and treated with interferon-β showed lower degrees of disease and lower average viral load compared to animals that were not treated, both in the lungs and extra lungs. The lack of drug interactions between lopinavir-ritonavir and interferon-β makes this combination of drugs attractive for clinical trials in COVID-19 patients. It is also suspected that a combination of lower doses of interferon-β with lopinavir-ritonavir can have a viral suppression effect with a lighter side effect than Lopinavir-Ritonavir alone with regular doses, although there are no conclusive results.

In rare cases, such as monoclonal gammopathy treated with interferon-β, systemic capillary leak syndrome can occur. Other unusual side effects from interferon-β administration are hypersensitivity reactions, pancreatitis, cytopenia, cardiomyopathy, and liver and thyroid dysfunction. Some interferon users had also reported some episodes of depression and even thought of suicide, so Interferon should be indicated for those who had serious depression or attempted suicide. Furthermore, there are concerns from some researchers, that the administration of interferon-β in patients with COVID-19 with severe and advanced symptoms can actually worsen the effects of cytokine storms. Thus, further research is needed with a greater number of patients and more specific parameters to confirm further the efficacy and safety of using these drug combinations (Lopinavir/Ritonavir and Interferon).

Chloroquine is an old, widely used anti-malaria drug that is being produced by many companies. Meanwhile, Hydroxychloroquine is an analog drug, known to have a better safety profile than Chloroquine in long-term use. Several studies have shown that the use of Chloroquine and Hydroxychloroquine was able to inhibit the SARS-CoV-2 virus in vitro, with antiviral effects that were observed more potent in Hydroxychloroquine. The mechanism of inhibition of Chloroquine against SARS-CoV-2 is thought to involve the ability of immunomodulation of cytokines release; acidification on the surface of the cell membrane, which inhibits viral fusion into cells; and inhibition of viral en-

zymes, such as polymerase and viral protein glycosylation. The use of Chloroquine for COVID-19 cases is reported to have been used by the national health committee in China, and the results show a decrease in disease progression and duration of symptoms of COVID-19 patients. However, the primary data of this study have never been published.

A clinical trial publication of this drug in France, an open-label study of 36 patients with COVID-19 showed the use of Hydroxychloroquine (200 mg 3 times a day for ten days) associated with increased loss of detection of SARS-CoV-2 RNA in swab specimens on the day six compared with those not treated with Hydroxychloroquine (70% vs. 12.5%). In this study, a combination with Azithromycin is believed to be able to provide additional effects on the administration of Hydroxychloroquine. However, some experts are concerned that the study design was not randomized, and six patients in the therapy group were not included in the analysis, of which five experienced severe conditions.

Despite limited clinical data, some clinicians still recommend the administration of Hydroxychloroquine (or Chloroquine) in patients with COVID-19 with severe conditions. In vitro data indicate that Chloroquine could inhibit the virus, but the dose required is usually high and can cause severe toxicity. In some cases, some serious side effects have been reported, such as QTc prolongation (causing arrhythmia), retinal toxicity, and even suicidal attempt. In some countries, as a result of "excessive" promotion of the use of Chloroquine, it has been indicated that there is an overuse of this drug without considering a safe dose and triggers the scarcity of this drug for other patients who really need this drug, such as patients with lupus. Therefore, large-scale research is required to test the effectiveness and safety of the use of these two drugs.

INA-RESPOND takes the initiative to join both the SOLIDARITY and ACTT trial and recruit some hospitals in Indonesia to participate in those studies. At least 22 hospitals across Indonesia agreed to join this trial, and currently, we have received the ethical review by Indonesian NIHRD and Approval of Clinical Trial by Indonesian FDA. There will be a waiver for approval of ethical clearance in each site, in order to ease the administration barrier, and this trial can be conducted as soon as possible. While we are waiting for the imported drugs from WHO, we are preparing the study activation and conducting regular TC call between site participants to disseminate the study protocols and make an agreement between clinical providers. Hopefully, with aggressive measures and massive participation throughout the globe, the cure for COVID-19 might be discovered soon.

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INA-RESPOND Newsletter

RACING TO DEVELOP VACCINES FOR SARS-COV-2

By: Herman Kosasih

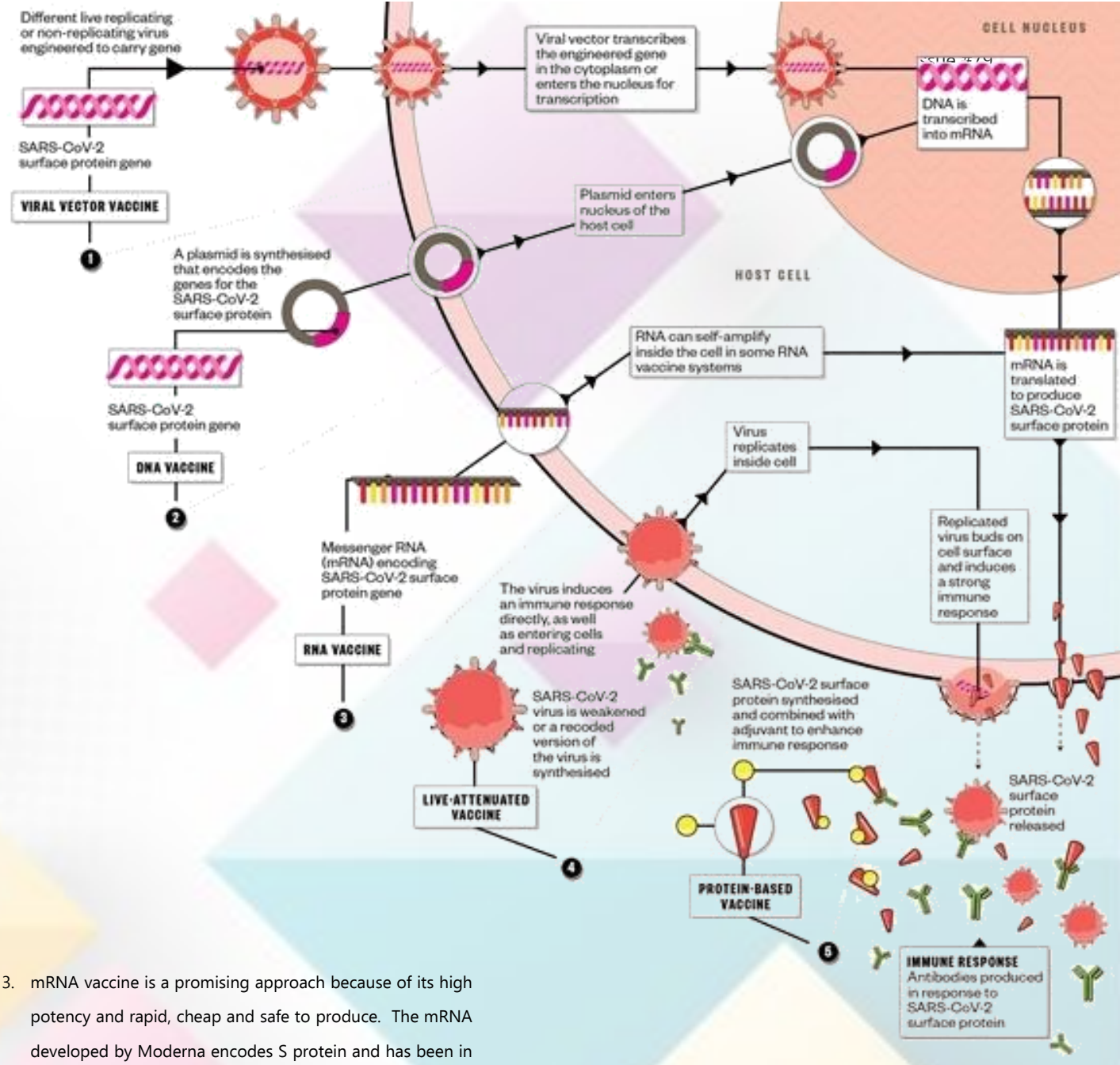
Indonesians are very familiar with vaccination, a.k.a *imunisasi* in Indonesian. Until the age of 12, children usually have received vaccination for 9 pathogens (5 bacteria and 4 viruses). These do not include dengue and influenza viruses which are optional and self-paid. Therefore, when SARS-CoV-2 finally 'arrived' in Indonesia and the number of Covid-19 cases keeps increasing, people clamor for the vaccine and ask when the vaccine will be available. The government has assigned Eijkman Institute to lead the consortium to find the seed vaccine that can be given to Biofarma for starting the production and conducting clinical trials. Biofarma is the only vaccine manufacturer in Indonesia and it has a lot of experience in producing vaccines for hepatitis B, seasonal influenza, polio, measles, and other pathogens. Prof. Amin Soebandrio, the Director of Eijkman Institute, emphasized the importance of Indonesia to be able to produce Covid-19 vaccine for two reasons. First, the production capacity of vaccine developers, particularly during pandemic, is limited. Therefore, each company will prioritize the needs of their country to protect their people. For example, there is rumor that the US President, Donald Trump was trying to spend $ 1 billion to ensure CureVac, one of the leading contenders to create a Covid-19 vaccine, exclusively produced for the USA. Second, the vaccine will be very costly during the pandemic. Without self-production, Indonesia has to spend approximately 51 trillion rupiahs to vaccinate half of the populations and it will take a few years to complete the vaccination program.

Although many experts are optimistic that Covid-19 vaccine will be available in approximately 18 months from now, vaccine development is a lengthy and expensive process. Usually, it takes many years to produce a licensed vaccine, because a linear sequence of steps, from pre-clinical trial and clinical trial (phase 1 to phase 3) has to be followed. Between each step, developers must stop for data analysis to ensure successful outcomes before moving forward to another step. In the past 30 years, the US FDA only approved 20 vaccines from almost 3,000 vaccines on clinical trials. Developing vaccines for pathogens that cause outbreaks or epidemics such as Ebola, Zika, MERS, or SARS is even more complicated and risky for developers as often epidemics ended before the vaccine was completely developed. Consequently, funding was re-allocated for other priorities and the program then stopped.

It is interesting that different platforms are being prepared, a combination of platforms that use advanced technology such as mRNA and DNA vaccines and a tried-and-true technology such as inactivated virus vaccines. The variety of plausible strategies for Covid-19 vaccine development is applauded by researchers as we do not know which vaccines are safest and going to work best.

The diagram above shows several types of vaccines that are currently under development:

1. Viral vector vaccine is a combination of the strong immunogenicity of live attenuated vaccines (the vector) and the safety of subunit vaccines to induce cellular immunity. Johnson & Johnson and CanSino use adenoviral vector platform with S protein antigen. First human trial has started in March, 2020.
2. DNA vaccine comprises plasmid DNA molecules, encoding one or more antigens. As they have to enter the nucleus, it may be risky for integration and mutation in the host genome. One of the developers, Inovio Pharmaceutical, plans to start the human trial in April 2020.



3. mRNA vaccine is a promising approach because of its high potency and rapid, cheap and safe to produce. The mRNA developed by Moderna encodes S protein and has been in human trial since March 2020. Other developers using this platform are CureVac from Germany.
4. Live-attenuated vaccines have multiple antigenic components and can potentially induce diverse immunologic effectors against the pathogen. Codagenix, Inc in collaboration with the Serum Institute of India, Ltd is going to start the human trial in August 2020.
5. Subunit/protein-based vaccines include one or more antigen with strong immunogenicity capable of efficiently stimulating the host immune system. It is safer, but requires adjuvants to elicit a strong protective immune response. S protein antigen is the most common subunit vaccine prepared by several institutions such as Novavax and Queensland University. Human trial is estimated to start by June 2020.

Referring to the timeline of the above vaccine, it is expected that Moderna and Johnson & Johnson vaccines will be given to 5,000 subjects in late fall and we will know whether the vaccines work in January 2021. To accelerate the development of vaccines during pandemics, it is expected that several steps can be done simultaneously in parallel rather than following the serial fashion. When a vaccine is safe and may provide good enough protection and durability to prevent a lot of death to health care workers and high risk population, a vaccine candidate might be made available before efficacy trials are completed.

Although we are in need of the vaccine, we have to ensure that vaccine is safe, i.e. will not result in paradoxical phenomenon, people who received vaccine will get more severe illness than people who did not receive the vaccine, as it happened with dengue, RSV or SARS-CoV vaccines. This immune malfunction may be explained by antibody dependent enhancement (ADE) theory and by the Th-2 immunopathology theory. 1) The ADE is very famous in dengue infection where sub-neutralizing antibodies from previous infection may enhance the subsequent infection. Some experts doubt, though, that ADE is relevant. No convincing evidence that humans can get recurrent infection with SARS-CoV-2. On the contrary, antibodies against SARS-CoV could also block SARS-CoV-2 infection. Also, ADE is unlikely to occur in this current coronavirus because the virus' target is respiratory epithelial cells, not the macrophages as in dengue virus infection.

2) Th-2 immunopathology is a cell-based enhancement where a faulty T cell response triggers allergic inflammation that is potentially damaging the airways. First, it was reported during a trial of RSV candidate vaccine where two children died from an unusual immune response. Severe damage in the lung tissues showed lots of neutrophil, eosinophil and cytokine. Researchers identified a similar problem during the development of SARS-CoV vaccine when immune cells of vaccinated animals attacked the lung tissue. They solved the problem by changing the antigen from the whole spike protein to only the receptor binding domain. Researchers believe that there is a potential for ADE, but Th-2 immunology is probably the main problem.

Since the number of cases is still rising in many countries with a total of > 1.5 million cases in less than 4 months, and significant mortality rate, vaccine is really needed particularly in countries with less healthcare resources when effective antiviral is still unavailable. Since SARS-CoV-2 is the third attack of Coronaviruses in the last 17 years, other coronaviruses in animals are ready to jump to humans. Therefore, learning from the mistakes in the past when halting the SARS vaccine development, vaccine development should be continued, even when the pandemic stop. As other pathogens may also become a threat, vaccines or platforms that are effective for prototype pathogens from various viral family or that can be readily adapted to new pathogens is very important.

Another alternative that researchers are studying is the use of a century-year vaccine for tuberculosis, BCG to reduce the risk of SARS-CoV-2 infection. The rationales of studying this vaccine are, first, BCG vaccination will boost immune body system that may reduce infections by bacteria, parasites and viruses, and second, epidemiology study reveals the incidence rate of COVID-19 is 100x less in countries where BCG vaccination is given. However, this estimation needs to be interpreted with caution as developing countries where BCG vaccination is usually given are not included in the analysis due to less reliable COVID-19 counts. Since the different rate may also associated with the behaviors such as how persistence of mask-wearing and social distancing in the population, we need to wait for the preliminary results from several studies that are currently conducted in the US, the Netherlands, and Australia.

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INA-RESPOND Newsletter

SCIENCE OF SUNBATHING – WHILE GETTING HAPPINESS NEEDS A BIT OF 'GUIDELINES.'

By: Aly Diana

Sunbathing provides many benefits for our well-being, but it poses some dangers as well. When we look at our social media in the last several days, there is some confusion out there. What are the main benefits of sunbathing? What is the best time for sunbathing? For how long? Should we worry about skin cancer? So, let's see what we should do for the 'best' results, avoiding the risks while getting most of the benefits.

There are three types of UV radiation: UVA, UVB, and UVC, which are classified according to their wavelength. They differ in their biological activity and the extent to which they can penetrate the skin. All UVA is transmitted through the atmosphere, and the earth's ozone layer absorbs all UVC and some UVB rays. So, most of the UV rays we come in contact with are UVA (~95%) with a small amount of UVB (~5%). UVA penetrates deeply into the dermis, while the epidermis almost entirely absorbs UVB.

Both UVA and UVB can cause damage to our skin and eyes. It may also enhance the development of skin cancer. The UV Index was created to measure the level of UV radiation; the higher the index, the greater the potential for damage, and the less time it takes for harm to occur. The UV index is divided into 5: Low (1-2), Moderate (3-5), High (6-7), Very High (8-10), and Extreme (11+). Sunburn is a sign of short-term overexposure, while premature aging and skin cancer are the side effects of prolonged UV exposure.

Nevertheless, UVB also has several benefits. It helps the release of nitric oxide, which stimulates vasodilation and lowers blood pressure); thickens the outermost layer of the epidermis and increases skin pigmentation (protecting the skin and deeper tissues from the deeper penetrating and damaging UVA rays while retaining benefits from UVB exposure); produces beta-endorphin; regulates circadian rhythms; and synthesizes vitamin D in our skin.

So, do we need sun (UVB) to get our vitamin D? Actually NO. The sun is not the only source of vitamin D, as we can get it from food (mainly from fatty fish and fish oil, less from beef liver, meat, egg yolk, and mushroom) and supplements. However, studies have shown that vitamin D deficiency and insuffi-

ciency are common globally. Reports from Mexico, South America, Europe, Asia, India, and even Africa suggest that more than 50% of the world population is at risk of vitamin D deficiency. People do not consume enough vitamin D-rich foods and supplement and do not expose to the sun long enough. Sufficient vitamin D increases calcium absorption, promotes musculoskeletal health, improves the immune system, and protects against some cancers. In contrast, vitamin D deficiency is associated with depression, seasonal affective disorder, and neurocognitive dysfunction.

Improving our diet and taking supplements is an excellent way to increase our vitamin D level. However, we need money for that, while the sun is free. The general recommendation to get vitamin D is to get a few minutes of sun exposure between 10 am to 3 pm (fair skin: around 3–15 minutes, dark skin: 15–30 minutes), with 40% of the skin area exposed (short sleeve top, short bottom). If we wear more clothes, then the length of the exposure should be longer. A study in West Java suggested continuous exposure for approximately 65 minutes for women wearing a hijab. The good news is, there is little evidence that sunscreen (SPF 30-50) decreases vitamin D concentration when used in real-life settings, suggesting that concerns about vitamin D should not negate skin cancer prevention advice. One thing to remember, the risk of skin cancer increases with prolonged exposure to the sun, especially when the UV index is very high/extreme (>7). Daily exposure of sun for 15-30 minutes for people with dark skin has not been proven to carry such a high risk for skin cancer.

So, this is the summary:

- If we only aim for happiness (just because we love the sun so much), we can go out when the UV index is low (mostly before 8 am and after 4 pm if we live in Indonesia). UV index for some countries can be accessed here: https://www.who.int/uv/resources/link/indexlinks/en/.
- If we aim for vitamin D synthesis, we can sunbathe between 10 am and 3 pm. Using sunscreen (SPF 30-50) is not a bad idea.
- If we must be out under the sun for a long time when the UV index is moderate or higher, please follow WHO/FDA suggestions to seek shade, use sunscreen, and wear protective clothing (including hat and sunglasses).
- If you feel too hot/red when you are sunbathing (which indicates that your skin has started to burn), go inside immediately, and have a cold shower (without soap).
- The standard glass window blocks all UVB but passes all UVA, so sunbathing behind a window is a bad idea.

Some considerations:

- UV index varies based on areas (including latitude and altitude), time of year (seasons), time of day, and the existence of clouds.
- Many surfaces reflect UV radiation and add to the overall UV levels we experience (fresh snow is a particularly good reflector and almost doubles a person's UV exposure, with seafoam reflects about 25%, sand 15%, and grass/soil/water 10%).
- The risk for cancer is also associated with genetics and type of skin. Some genes promote, and others protect against cancer. Also, different types of skin have different risks. For example, people with fair/pale skin who quickly get sunburn and don't tan are more likely to get sun-related skin cancer.
- As for exposure, the "dose" and its timing are crucial. Recommended time (minutes) for sunbathing also depends on the total body surface area exposed to the sun. Also, several studies have suggested that suddenly getting a lot of sun exposure is more dangerous than steady exposure over time.

Like other things in the world, no answer will stay forever. These simple 'guidelines' may change once more studies and more evidence are collected.

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INA-RESPOND Newsletter

EXERCISE: HOW MUCH IS TOO MUCH?

By: Ria Lestari

Exercise is a major component of a healthy lifestyle, and the benefits of regular physical activity are well established. There are so many ways to exercise, such as yoga, swimming, weight training, jogging, cycling, walking, rock climbing -- and they all have unique benefits. Outside of physical changes like building muscle and losing fat, exercise can help with mood, sleep, and stress management.[1] However, there is such a thing as overdoing it when it comes to physical activity.

The latest research in 2016 by Mayo Clinic Proceedings suggests that exercising too much may increase your risk of dying from cardiovascular disease.[2] For the study, researchers looked at the data on about 2,400 heart attack survivors who participated in the National Runner's and Walker's Health Studies and assessed whether the participants' exercise habits were related to mortality. (The reason they looked at heart attack survivors is that there were not enough "cardiac events" among the healthy runners to examine the effect of exercise on cardiovascular mortality.) After controlling factors like sex, age, education, red meat intake, fruit intake, alcohol consumption, baseline smoking status, aspirin use, medications for high cholesterol, hypertension, and diabetes, researchers found that exercise was inversely correlated with mortality risk up to a point.

After 10.4 years, 526 of the participants died—and more than 70 percent of the deaths were related to cardiovascular disease. People who did the exercise equivalent of running 15 to 23 miles per week had a 50 percent lower risk for cardiovascular disease-related mortality than those who infrequently exercised. Moreover, those who ran 23 to 30 miles per week decreased their risk by 63 percent. However, beyond 30 miles of running or 46 miles of brisk walking per week, though, there was a 2.62-fold increased risk of dying of cardiovascular disease (that's about the same risk as with people who didn't meet the minimum exercise guidelines).

Extreme endurance exercises, like ultra-marathons, may also lead to heart damage, heart rhythm disorders, and enlarged arteries in some people. Experts believe extreme endurance puts extreme demands on the cardiovascular system. One study from 2017 found that repeated, intense exercises can "remodel" the heart, thicken the muscle's walls and scar tissue.[3]

Another study showed that women are less likely to have a heart attack or stroke if they are physically active at least once a week.[4] But that risk of heart attacks and strokes shot up for women who exercise strenuously every day. So, excessive exercise does not provide more benefits than moderate exercise. And it could be riskier. Women are at particular risk for what is known as the Female Athlete Triad (FAT) that includes: changes of menstruation, bone mineral loss, and low energy availability. These symptoms usually arise from a combination of over-exercise and calorie restriction.

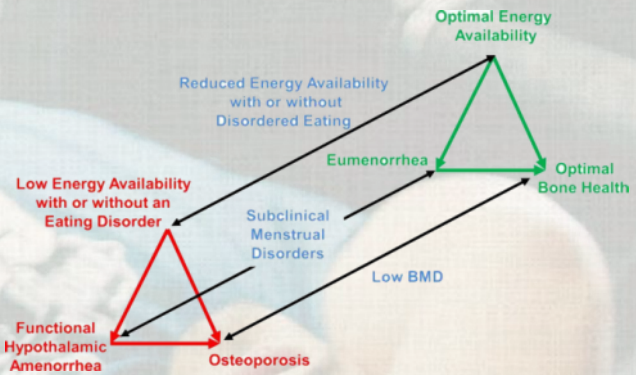

Figure 1. In red, the three related components of the female athlete triad: Eating too little affects menstrual status, and in turn, calorie availability and menstrual status influence bone health. In green, optimal health is indicated by adequate energy availability, regular periods (eumenorrhea), and good bone health.[5]

For men, intense exercise has been shown to decrease libido. Possibly due to physical fatigue and lower testosterone levels. For both men and women, over-exercise raises the risk of overuse injuries, like tendinitis and stress fractures. These injuries result from repetitive trauma. Your immune system can likewise suffer.6 While moderate exercise can improve your immune system, excessive exercise can suppress it.

So, how much exercise is too much? And how do we know when we need to rest?

According to the American College of Sports Medicine, to maintain your general health, most adults should aim to squeeze in 150 minutes of moderate aerobic exercise or 75

minutes of vigorous aerobic activity each week. It's not easy to keep track of how much you're exercising in a week, but aim for about 30 minutes a day, five days a week to keep things in check — more if you're trying to lose weight. If you are doing high-intensity exercises, limit yourself to no more than three times per week.[7]

How much exercise you need (and how much is too much) is different for everyone. Below are several signs if you have too much exercise:

a. Dehydration

Exercise creates an increase in body temperature, which is cooled by sweating. If your body is not properly hydrated, it is not able to cool itself properly. If we exercise outside in extreme heat, it is even more dangerous without enough fluid intake. Fluids help with muscle contraction and blood flow – the two things that are necessary for your body to receive the full benefits of physical activity. Physical activity such as swimming requires proper hydration even when you do not feel hot or thirsty.

Drink 6-8 glasses of water a day, at least. If you are working out, chances are your body will need a bit more fluid. The best way to ensure proper hydration is to drink plenty of fluids not only during the workout but also before and after any physical exercise. Drinking a few glasses of water several hours before training allows your body to absorb the fluid and prepare itself for the upcoming stress. Drinking water during exercise helps maintain safe body temperature and drinking water after the workout helps your muscles to recover. If you are working out for more than an hour, you may want to drink fluids that replace electrolytes (i.e., sports drinks).[8] Remember to end your workout early if you start experiencing symptoms like dizziness, vomiting, nausea, headaches, and muscle cramps.

b. Overreaching and Overtraining

If you push yourself at the gym to reach certain fitness goals, you may be working against yourself. Overreaching is a state of excessive volume or intensity of exercise, resulting in decreased sport-specific athletic performance. When training loads reach an athlete's individual "tipping point," he or she can be considered overtrained or overreached. With appropriate rest and recovery (and the absence of excessive stress), performance can be increased through supercompensation despite overreaching with the athlete suffering only a temporary performance impairment.[9]

Overtraining is a particular and severe condition when overtraining without adequate rest and recovery leads to performance decrements that last for >2–3 months, coupled with a mood disturbance. Synonyms used in the literature around overreaching include staleness, burnout, failure adaptation, under-recovery, training stress syndrome, unexplained underperformance syndrome, muscle failure syndrome, and excessive exercise.[10]

c. Menstrual Disturbance

Missing your period may sound like a blessing in disguise, but it may also be a sign that you have been over-exercising. This usually happens because the combination of intense exercise and low calories intake causes the body to enter "shut-down mode," where it turns off all functions that are not necessary to survival — including the reproductive system. Women can lose an estimated 2-3% of bone mass per year if left untreated.[11, 12]

Unfortunately, though the break from your period may be appreciated, it can have long term repercussions. Since your body is without estrogen while your reproductive system is in shut-down mode, it can leave you open to issues down the road like osteoporosis, infertility, and atrophy of the breasts and vagina.

CONCLUSION

Exercise has been shown to have many health benefits, both physically and mentally. It may even help you live longer. There is no question that you should still strive to be physically active. However, getting the recommended amount of exercise is important. Getting more than that is okay if you have a specific goal in mind and are continuing to give your body enough time to rest and recover between workouts.

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