INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

November 2018

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General Hospital

Caffeine in My Coffee:
My Love, Should I
Keep or Let You Go?

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2018

Next Generation Sequencing (NGS) Workshop

@Ars Longa, Badan Litbangkes, Building 3, Level 3

Jakarta

INA-RESPOND newsletter

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INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: ANANDIKA PAWITRI, EKA WINDARI R., LOIS E. BANG, MARIA INTAN JOSI, M. IKHSAN JUFRI, VENTY MULIANA SARI

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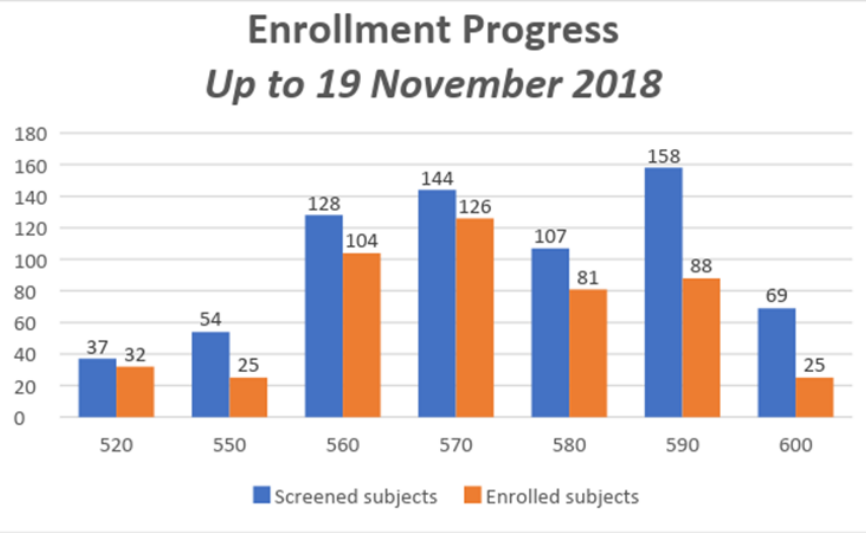
SCREENING AND ENROLMENT

Up to 19 November 2018, all seven sites had enrolled a total number of 481 subjects. The sites enrolled 69% of the screened patient (481 enrolled subjects from 697 screened patients).



ENROLLMENT HALT PREPARATION

Based on the result of the previous interim analysis meeting, all of the TRIPOD study teams are preparing the site to face the enrollment halt per 1 December 2018. The secretariat has compiled the estimated working hours of each site RA after the enrollment halt in order to calculate the workload for TRIPOD study. The site RA will be directed to be prepared for an involvement in another study that is running at their site, such as PROACTIVE study or PEER PePPes study. The enrollment halt notification for all Ethical committees has been prepared and submitted too on 22 November 2018.

TRIPOD STUDY ABSTRACT PUBLICATION 2019

In 2019, the INA-RESPOND secretariat will facilitate TRIPOD Study team members whose abstract has been accepted in an International conference. TRIPOD study core team has distributed the list of upcoming events where teams can participate in next year and encourages all site team, especially PIs/Co-PIs to submit abstracts of TRIPOD study results. PIs/Co-PIs who have ideas or had already submitted an abstract should notify Secretariat team at least six months prior to the conference.

REFRESH of PBMC LABORATORY TRAINING

There are several activities for PBMC training in site 580 and site 570. Ms. Gusti from INA-RESPOND Reference Lab conducted a site visit to site 580 on 19 November 2018 to give PBMC training for laboratory staffs with new method. Meanwhile, on 6-7 November 2018, dr. Myrna and Lab technician from site 570 visited our Reference Lab in Tangerang to receive a refresher course on PBMC.

CONGRATULATIONS!

Congratulations to Dr. dr. Erlina Burhan, M.Sc, SpP (K). We hope it's not too late to congratulate you for the well earned promotion to the post of *Member Board of Director the International Union Tuberculosis and Lung Disease*. We wish you the best in this new term of office.

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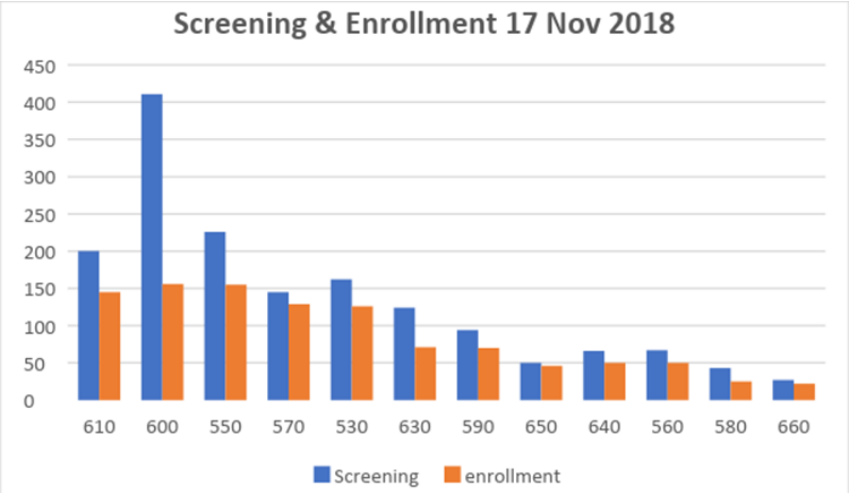
By 17 Nov 2018, all the 12 sites as shown in the figure had enrolled 1,045 subjects consisted of 49 pediatrics and 996 adults. The sites enrolled 64,7% of the screened patients (1,615 screened patients).



The enrollment failure rate was 35,2% from total screening due to some reason as stated in the table below.

For the Site Monitoring Visit, 3rd SMV had been conducted at site 610/RSU Kabupaten Tangerang on 29, 30, and 31 October 2018 and the 2nd SMV at site 600/RSUP Dr. Adam Malik on 21-23 November 2018. We also planned to do a 2nd SMV to site 570 on 18-21 Dec 2018.

Currently, we are also preparing for the Site Preparation Visits to site 520/RSUP Sanglah, Site 540/RSPI Sulianti Saroso, and site 510/RSUP Dr. Hasan Sadikin. Hopefully, we can conduct the Site Preparation Visits to these sites in December 2018. We have also conducted a site assessment visit to RSUD Zainoel Abidin on 5 November 2018. In addition, we are still working for the site assessment of RSUD Jayapura and RSUD Merauke.

Reason	610	600	550	530	570	630	590	650	640	560	580	660	Total
HIV-negative	1	-	1	-	-	1	-	-	-	-	-		3
Refuse to consent	2	-	2	2	4	-	4	-	-	2	-		16
Unwilling to comply with the study procedures	1	20	-	5	3	-	-	1	-	10	3		43
Plans to move away	-	8	4	6	-	1	3	-	2	2	-		26
Others:	51	227	64	23	9	51	17	3	14	3	15	5	482
A. No show	27	224	16	14	4	32	12	-	3	1	2	2	337
B. Busy (in a hurry)	16	3	26	8	4	4	1	3	11	2	10	3	91
C. Not cooperative	-	-	1	-	-	-	-	-	-	-	-		1
D. Has been enrolled	6	-	17	-	1	9	4	-	-	-	-		37
E. Unwell	-	-	2	-	-	-	-	-	-	-	-		2
F. No referral letter from others health facilities	-	-	-	1	-	-	-	-	-	-	-		1
G. Equipment trouble	-	-	-	-	-	6	-	-	-	-	-		6
H. Participated in other CT											3		3
I. Hospitalized	-	-	2	-	-	-	-	-	-	-	-		2
m. Suspect HIV patient	2	-	-	-	-	-	-	-	-	-	-	-	2

INA-RESPOND Newsletter

Site Profile: Dr. Cipto Mangunkusumo General Hospital

By: AINUM JHARIAH HIDAYAH

From left to right : dr. Bramantya Wicaksana, Ms. Ainum Jhariah Hidayah, SKM, M. Epid, Ms. Wusthi Ali Chasana, Ms. Neneng Yuliani, Dr. dr. Evy Yunihastuti, SpPD-KAI, Ms. Madyaningati

Dr. Cipto Mangunkusumo General Hospital, Faculty of Medicine, University of Indonesia is one of the sites in INAProactive Study. We started our first subject enrollment in May 2018. This site is located in Jakarta, which is the capital city of Indonesia. This site is called Site 530. INAProactive is one of INA-RESPOND studies in this site.

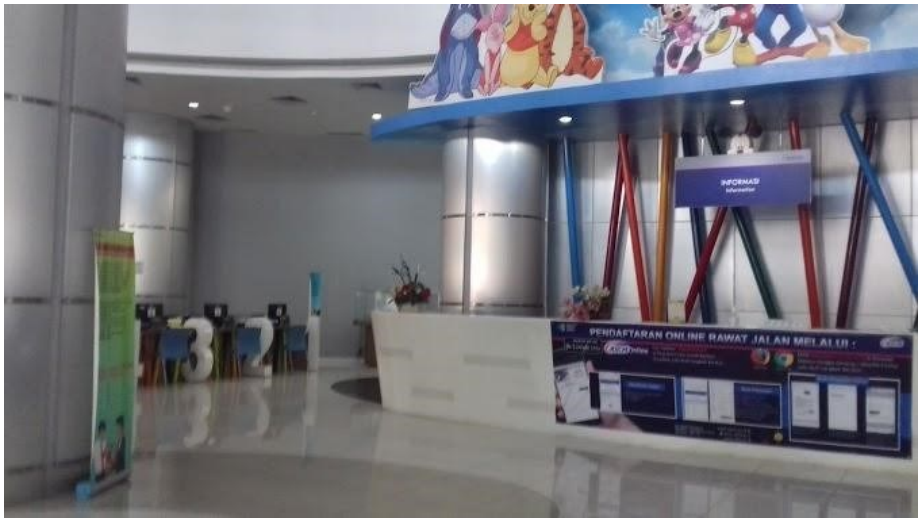
This study involves many departments and polyclinics in this site, such as Integrated HIV Services, Pediatric Allergy and Immunology Polyclinic in Kiara Mother and Child Building, and Clinical Pathology Laboratory. Our site room, where we put all of the documents is located in front of HIV Integrated Services. Our team consists of nine people. Eight of us are women and there is only one male, but he is the most excited and talkative person in this team. The following are the descriptions of our team members.

Prof. dr. Pratiwi Sudarmono, SpMK(K), PhD is one of the headmasters and professors of Microbiological Science in the Faculty of Medicine, University of Indonesia. Her achievement in the Faculty of Medicine is countless. She has served as a deputy dean 1 for two periods. Besides that, she is familiarly known as a Clinical Microbiology Specialist, and she is still an active

lecturer of the Department of Microbiology, Faculty of Medicine, University of Indonesia.

Dr. dr. Evy Yunihastuti, SpPD-KAI is an energetic doctor. She is the Allergy and Clinical Immunology Consultant. She received an award as a very productive researcher in the Faculty of Medicine, University of Indonesia. She has done many researches about HIV, most of them has been published in the National and International Journals. Because of her productivity, she also works as a research coordinator in the Department of Internal Medicine, Faculty of Medicine, University of Indonesia. She is very busy but she always visits the RA in site room to have discussions.

Pokdisus Polyclinic Most of our activities are done here because our room is located in front of HIV Integrated Services. We do screening and enrollment of adult patients here. This polyclinic is open from Monday to Friday.



Pediatric Allergy and Immunology Polyclinic This polyclinic is located on the second floor of Kiara Mother and Child building. We do screening and enrollment of pediatrics patient here. This poliyclinic is open on Tuesday and Friday.

dr. Nia Kurniati, SpA(K) is a beautiful and friendly doctor. She is not only a Pediatrician, but also the Allergy and Immunology Specialist for children. She manages the finance of INA-RESPOND researches in this site. She always takes time to visit and discuss about pediatric patients with the RA team in the site room.

dr. July Kumalawati, DMM, SpPK(K) is one of educational staff (lecturers) at the Clinical Pathology Department, Faculty of Medicine, University of Indonesia and Dr. Cipto Mangunkusumo Hospital. She also works as a coordinator of National Reference Laboratory for HIV-Testing at the Department of Clinical Pathology. She is an energetic doctor with a lot of work

Clinical Pathology Laboratory

This laboratory is located on the 7th floor of the Integrated Heart Center building. We analyze patients' viral load data and put the study freezer here.









everyday. She has white skin and wears glasses. In INAProactive, she is responsible in control patient laboratory result.

dr. Bramantya Wicaksana, who is familiarly known as dr. Bram, is a doctor who is very friendly. He has finished his internship program in Kalimantan. He is an active person.

Ainum Jhariah Hidayah, a.k.a. Ainum, completed her Epidemiology Master Program in the Faculty of Public Health, University of Indonesia. Her master thesis was about Survival in HIV Patients. Being involved in clinical research is her first experience, so she hopes that she can do her best in this study. In site 530, she is also responsible in finance.

Neneng Yuliani. She is the third research assistant in this site. She is the oldest Research Assistant (RA). Sometimes, she always gives attention to the other RAs. She is well known by many patients because before she joined INAProactive, she worked as HIV-Patient associate. She helps the team to communicate with the patients. Her hobby is singing. The site room will not be quite because she always sings a song.

Madyaningati. She is called Bundo. She is our laboratory technician who is very good at drawing blood. She has straight hair and is always well-dressed. Besides doing laboratory examinations on general patients, she also helps in some researches on Pokdisus HIV because she is the only laboratory technician in Pokdisus Polyclinic, which makes her very busy every day.

Wusthi Ali Chasana. She is the research nurse in this site. She wears glasses. She helps our laboratory technician in drawing blood, blood sampling, and other laboratory needs.

From left to right (top to bottom):

SITE 530 TEAM MEMBERS

NSC : Prof. dr. Pratiwi Sudarmono, SpMK(K), PhD
PI : Dr. dr. Evy Yunihastuti, SpPD-KAI
Co-PIs : dr. Nia Kurniati, SpA(K)
dr. July Kumalawati, DMM, SpPK(K)
RA : dr. Bramantya Wicaksana
Ms. Ainum Jhariah Hidayah, SKM, M. Epid
Ms. Neneng Yuliani
Lab Technician : Ms. Madyaningati
Research Nurse : Ms. Wusthi Ali Chasana

INA-RESPOND Newsletter

Corrective Actions and Preventive Actions (CAPA)

By: ANANDIKA PAWITRI, LOIS EIRENE BANG, MARIA MILA ERASTUTI

In our September 2018 newsletter, we mentioned that there were a lot of deviation cases under protocol implementation categories. Interestingly, 95% of them are missed procedure/assessment of the protocol, and a lot of them can be avoided. Like in any other projects, something may go wrong that could affect the project's quality. When that happens, the issue must be resolved in a timely, effective, and compliant manner.

What should we do when a deviation has occurred?

The answer to the question above is CAPA. CAPA stands for Corrective Actions and Preventive Actions. Corrective Action is the elimination of the cause or causes of an existing nonconformity or undesirable situation to prevent recurrence. Preventive Action is the identification and elimination of the causes of potential nonconformities to prevent occurrence.

The following is an illustration to better understand CAPA.

We brush our teeth every day to prevent cavities. This is called taking a preventive action. A cavity appears although you brush your teeth everyday, and now you are in pain. You go to the dentist to get a filling, and the pain goes away. Going to the dentist and getting a filling are corrective actions.

How do we implement CAPA when we find a protocol deviation?

Corrective Actions

The root cause of the nonconformity needs to be identified and documented.

The effect of the nonconformity should be analysed to determine its impact and the actions required to correct or neutralize the damage or possible damages.

The entire system needs to be scanned to ensure that the nonconformity does not occur in other areas.

The actions that will prevent the nonconformity from reoccurring must be implemented, and follow-ups on the actions must be done to determine their effectiveness.

Preventive Actions

Proactive actions, such as risk assessments, failure modes, and effects analysis, must be taken to identify potential nonconformities

The development of work instructions, documented procedures, and training are the examples of actions that are performed to prevent nonconformities.

Other activities that are regularly carried out and are part of the preventive action process are audits, management reviews, and inspections.

Example 1: Missed procedure in PROACTIVE Study

A 19-year-old subject with initial ABC was enrolled at site X on 7 November 2015. There was no documentation for HIV testing result based on the medical record.

Lab Technician (LT) took the subject's blood sample on 7 November and she found out that the CD4 cartridge was out of stock, but due to her busy schedule, she forgot to tell the Research Assistant (RA). RA found out that the cartridges were out of stock the following day while he was completing the CRF. RA came to LT to get a confirmation and also found out that the HIV-1L Viral Load (VL) cartridge almost expired (in a week).

Corrective Actions

Find the root cause

The inventory form was not filled in regularly by LT. Therefore, LT did not know the actual remaining stock. LT and RA did not ensure the availability of CD4 cartridge at site. RA did not actively check and only wait for information from LT. Although preparing cartridges is LT's task, RA is responsible for checking the availability of these cartridges, as listed in Authorized Signature and Delegation Log (ASDL) and study specific SOP.

The nonconformity causes the CD4 testing for this subject on baseline visit non-existent, which is categorized as minor protocol deviation.

Need to be checked:

From several subjects on the same date, is there a subject that has no CD4 examination results? Check the enrolment log, SDW, CRF, and supplies and inventory log.

Are there other supplies that will run out of stock or are already out of stock? Check the stock of each supply in the refrigerator and compare it with the stock number in Supplies And Inventory Log (SIL).

Are there other supplies that will expire or have already expired? Check the stock of each supply in the refrigerator and compare it with the stock number in SIL.

The action items to correct the deviation are:

Update SIL every time a deviation is identified, and complete all the cartridge usage from the first subject to ensure the total CD4 examination that has been done and how many have not.

Fill documents: CRF page 1,300 deviation log, protocol deviation log, and upload it into INA-RESPOND portal and archive it into Site Regulatory Binder (SRB)

Follow up the actions to determine the effectiveness: will a similar deviation happen again later? Whether the form has always been filled?

Preventive Actions

Proactive actions

Since RA is assigned to ensure that the study runs well at site, RA must work together with LT to check supplies regularly (e.g. monthly basis of supplies at site)

Define procedure and working instructions

RA must define procedure or working instructions to be performed by LT regarding the procurement of supplies. These procedures can be/ for example:

- LT must complete supplies and inventory log every day
- LT must inform RA about all laboratory supplies that need to be requested each end of the month, and RA will send a re-supply request to INA-RESPOND Secretariat. In this case, the HIV-1 VL cartridge must be ordered immediately without waiting for the end of the month, not following the normal procedure.
- LT & RA must check the number of subjects in the enrolment log and SIL to ensure the suitability of the number of supplies used every day.

Do not forget to document all implemented CAPA and their status, and review your CAPA when a same/similar deviation happens again, starting the process from the first step (find the root cause of your problem). This will help to determine the real cause of your problem.

Finally, we now know why CAPA is important. It helps us to ensure that problems are detected and resolved at the right time, as well as prevented from happening again in the future.

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https://www.fda.gov/iceci/inspections/inspectionguides/ucm170612.htm

https://www.fda.gov/downloads/training/cdrhlearn/ucm421767.pdf

ISO/IEC 17025:2005 General requirements for the competence of testing and calibration laboratories

IDWeek at Moscone Center, San Francisco, USA

3-7 October 2018

INA-RESPOND Newsletter

REPORT

IDWeek: Advancing Science, Improving Care

By: NUGROHO HARRY SUSANTO, NURHAYATI

IDWeek is an annual scientific meeting where infectious diseases professionals meet, share experiences, and develop collaborations. With the theme "Advancing Science, Improving Care", IDWeek features the latest science and bench-to-bedside approaches in prevention, diagnosis, treatment, and epidemiology of infectious diseases, including HIV, across the lifespan.

IDWeek is a joint annual meeting of the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS).

IDWeek is geared toward healthcare professionals in infectious diseases and healthcare epidemiology and prevention, including researchers, clinicians, quality and patient safety practitioners, epidemiologists, and public health officials, including those who see HIV and pediatric patients. It is a must-attend meeting for professionals who want to stay current, apply state-of-the art science to clinical care, and excel in their own careers.

This year, IDWeek was held on 3-7 Oct 2018 at Moscone Center, San Francisco, California. The meeting was attended by ± 7,500 health care professionals in infectious diseases and healthcare epidemiology and prevention, including researchers, clinicians, quality and patient safety practitioners, epidemiologists, and public health officials, including those who see HIV and pediatric patients. ± 140 exhibitors from pharmacies and hospitals joined the meeting.

INA-RESPOND presented two posters at IDWeek 2018. One from INA-102 TRIPOD, titled "Drug-Resistant Tuberculosis (DR-TB), Comorbidities, and Risk Factors Identified in a Prospective Multicenter Cohort Study in Indonesia", which was presented by Nugroho Harry Susanto from the INA -RESPOND secretariat. In this poster,

we presented our findings that the number of DR-TB was higher than our estimation. Our estimation itself was based on WHO estimation of multi-drug-resistant TB (MDR-TB) number in Indonesia. Some people were interested in the number of DR-TB from our study.

Another poster from INA-201 Pneumonia in Pediatric patients, titled "Biomarkers in Different Etiology of Pneumonia in Pediatrics in Indonesia", was presented by Nurhayati from the INA-RESPOND secretariat. We showed multiple biomarkers between viral pneumonia and bacterial pneumonia in children. We received some comments about our results and suggestions that we could use a different cut-off based on their experience.

One of the sessions on TB, "Testing Diagnostics for TB", was started by highlighting the gap in diagnosing TB cases and even lower diagnosed multidrug-resistant TB (MDR-TB). The session discussed the current progress in TB diagnosis to bridge this diagnostic gap. Some of the diagnostic test in progress could diagnose multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). There is also a possibility to diagnose TB from other specimens such as rectal swab and stool swab, which are beneficial to diagnose TB in children, although using these kinds of specimen still have a low sensitivity.

Indonesia also has a large gap in diagnosing TB cases. Indonesia is even in the top three countries, with 16% gap between TB incidence and reported cases according to WHO TB Global Report 2017. This large gap is one of the reasons why INA-102 TRIPOD is needed in Indonesia. Although INA-102 TRIPOD is not the representative of general population in Indonesia, the high number of DR-TB and the large gap of diagnosed TB cases means that there are a high number of undiagnosed DR-TB in the population of Indonesia.

Besides Tuberculosis, many interesting topics were also presented such as antimicrobial stewardship, Microbiome, HIV infections, Healthcare epidemiology, Pediatric infectious diseases, Pediatric immunizations, and Respiratory infections.

We thank INA-RESPOND for giving us this great opportunity to join the meeting.

INA-RESPOND Newsletter

Infectious Disease News

By: M. HELMI AZIZ

This month's article will give us short news updates on baloxavir marboxil and dolutegravir, two drugs used in influenza and HIV treatment .

Baloxavir marboxil for influenza treatment

Influenza is an acute respiratory infection caused by influenza virus. Despite the availability of influenza antiviral and vaccines, influenza remains as a serious public health threat worldwide. Influenza drugs targeting neuraminidase, neuraminidase inhibitors (NAIs), are the mainstay of antiviral treatment for influenza infections [(1)]. However, NAIs-resistant influenza virus (NA/H274Y) has been reported, and it creates an urgent need of novel drugs against influenza virus [(1)].

The heterotrimeric influenza RNA polymerase, which comprises the sub-units PA, PB1, and PB2 protein, plays an essential role in the viral replication and transcription and are considered to be the new anti-influenza drug targets. Baloxavir marboxil (previously known as S-033188) is a first-in-class antiviral prodrug that is metabolized to a small molecule active form (baloxavir acid) and is able to suppress influenza viral replication [(1-3)]. In contrast to NAIs which inhibit the release of new influenza virus particles, baloxavir marboxil works as selective inhibitor of influenza cap-dependent endonuclease and prevents transcription to occur [(1-3)]. Baloxavir marboxil has shown a nanomolar antiviral activity against both influenza A and B virus in vitro, including the stratins that are resistant with the available influenza antiviral agents [(2)].

Phase 2 and phase 3 randomized control trials were

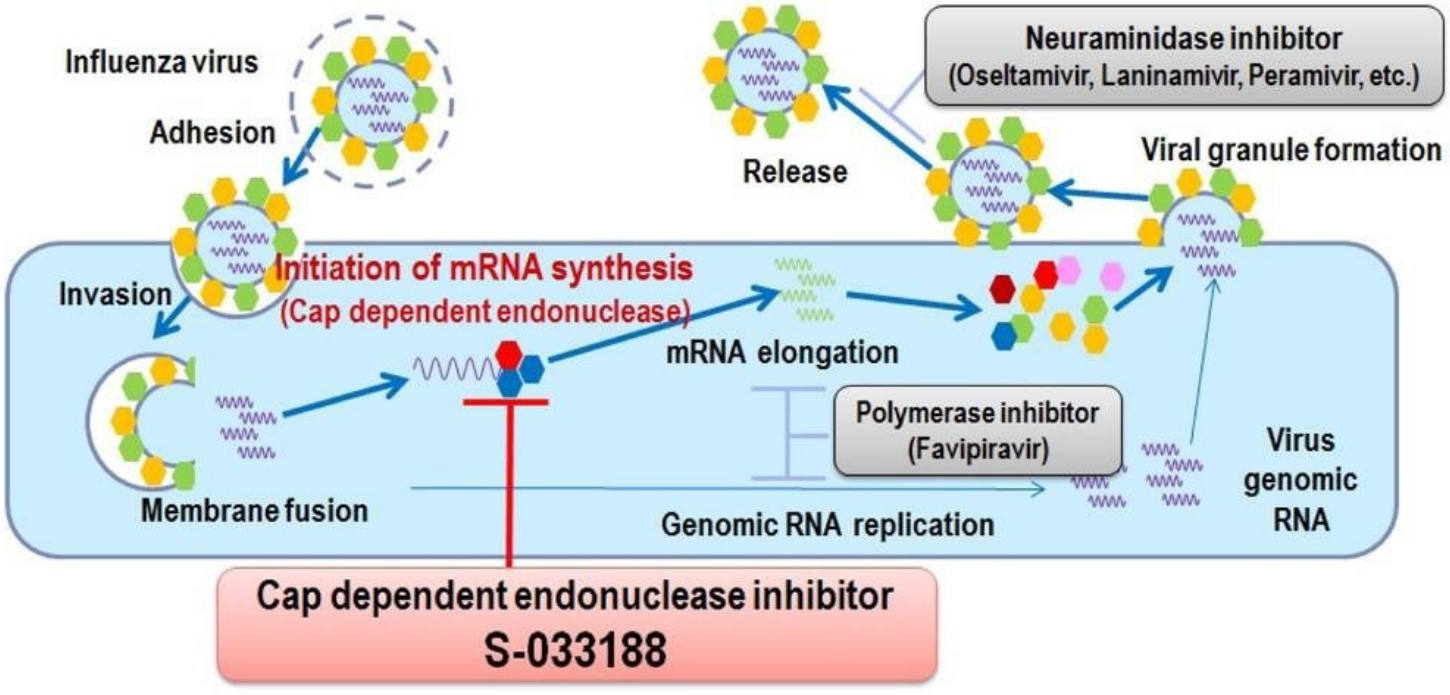
conducted in Japan and the United States [2]. The phase 2 trial was a double-blind, dose-ranging, placebo-controlled, and randomized trial of single dose of baloxavir marboxil (10, 20, or 40 mg) or placebo conducted on Japanese adults (20–64 years old) with acute influenza infection [2]. The median time to the alleviation of influenza symptoms in Japanese adults was 23.4–28.2 hours shorter in baloxavir group than in the placebo group [2].

The phase 3 trial, CAPSTONE-1, was a double-blind, placebo- and oseltamivir-controlled, randomized trial conducted on influenza-like illness outpatients (12–64 years old) in the United States and Japan [2]. The dose of oseltamivir was 75 mg b.i.d for 5 days; meanwhile, a single dose of 40 or 80 mg baloxavir marboxil was administered depending on the patient's body weight [2]. The median time to the alleviation of influenza-like illness symptoms was 53.7 hours in the baloxavir group (similar to oseltamivir group) and 80.2 hours in the placebo group [2]. In addition, in the baloxavir group, the viral reduction was observed on day 1 after the drug administration than in the placebo or oseltamivir group [2]. Adverse events were reported to be lower in baloxavir marboxil group (20.7%), than in the placebo group (24.6%) or the oseltamivir (24.8%) group [2]. However, there was an observation of the emergence of polymerase acidic protein variants that could reduce susceptibility to baloxavir in 2.2% and 9.7% of baloxavir recipients in the phase 2 and phase 3 trial subjects, respectively [2]. In conclusion, the trials showed that a single-dose of oral baloxavir marboxil was associated with clinical benefit and antiviral activity in patients with uncomplicated influenza. In addition, baloxavir marboxil could be a treatment option for influenza virus strains which are resistant to other influenza drugs.

Dolutegravir and neural tube defects

Birth outcome surveillance aimed to evaluate the prevalence of neural tube defects associated with antiretroviral (ARV) exposure from the time of conception (the risk period for neural tube defects ends approximately 28 days after conception) was conducted by Botswana Harvard AIDS Institute Partnership at eight government hospitals since August 2014 [4]. In May 2016, Botswana changed its first-line ARV regimen from tenofovir/emtricitabine/efavirenz to tenofovir/emtricitabine/dolutegravir for all adults [4]. The change of regimen allowed the surveillance to observe the dolutegravir association on neural tube defects from the time of conception [4].

The birth outcome surveillance reported that the risks of adverse birth outcomes or congenital abnormalities of dolutegravir-based regimens were not higher than efavirenz-based regimens after conception (including therapy initiated during the first trimester of pregnancy) [4]. However, the



number of neural tube defects was higher than expected among infants who were born from women who used dolutegravir-based regimens before conception [4]. An unplanned interim analysis was performed during the surveillance to compare the prevalence of neural tube defects among infants who were born to women who had been treated with dolutegravir-based regimens from the time of conception with the prevalence from other groups [4].

89,064 births were included in the Botswana birth outcome surveillance in which 88,755 births (99.7%) had an infant surface examination that could be evaluated for the diagnosis of neural tube defects [4]. Eighty-six (0.1%) cases of neural tube defects were identified, which consisted of 42 cases of meningocele or myelomeningocele; 30 cases of anencephaly; 13 cases of encephalocele; and 1 case of iniencephaly [4]. Four of 426 (0.94%) infants who were born from HIV+ women, who had been treated with dolutegravir-based regimens from the time of conception, had neural tube defects (encephalocele, myelomeningocele, iniencephaly, and anencephaly) [4]. In comparison, neural tube defects occured in 14 of 11,300 (0.12%) infants who were born from HIV+ women, who had been treated with non-dolutegravir regimens from the time of conception; 0 of 2,812 infants (0.0%) from women who had been exposed to dolutegravir-based regimens, that started during the pregnancy; and 61 of 66,507 (0.09%) in HIV-uninfected women [4]. However, more data were needed to confirm whether dolutegravir-based regimens from the time of conception contributed to the development of neural tube defects [4].

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INA-RESPOND Newsletter

Abs Are Made In The Kitchen

By: EDRICK PURNOMO PUTRA

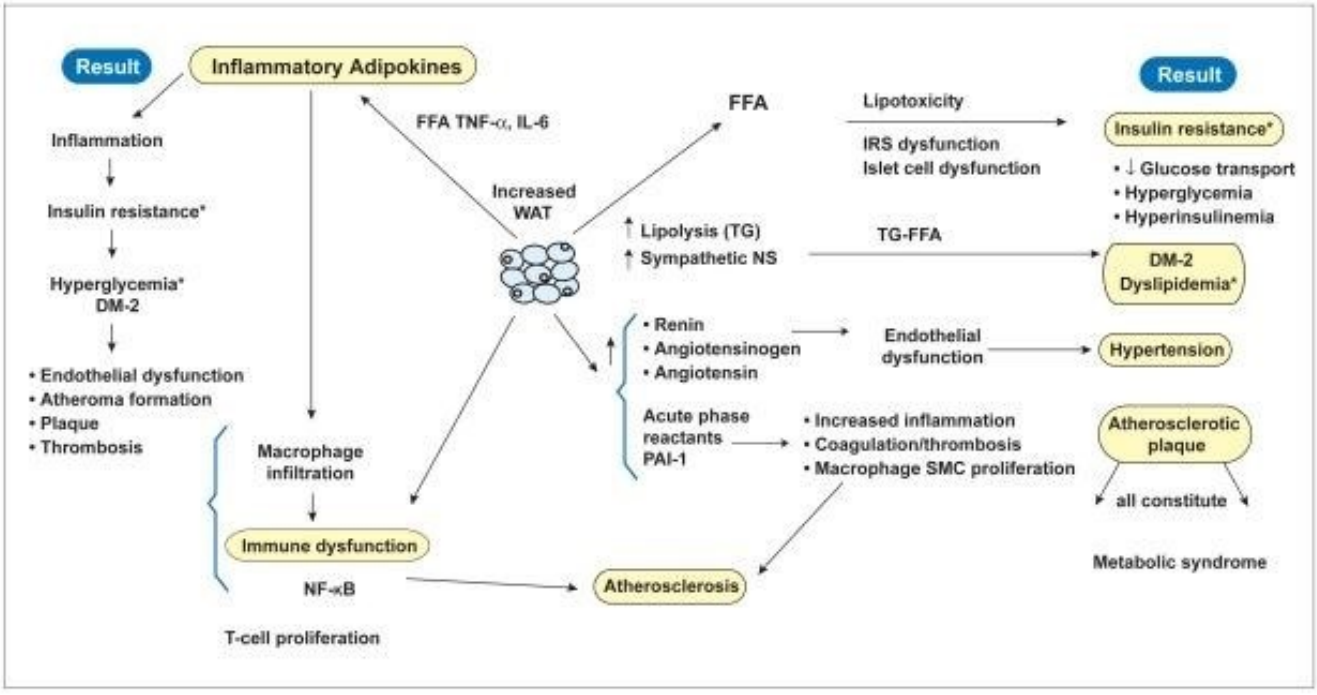
Name : dr. Edrick Purnomo Putra

Occupation : Resident doctor at University of Indonesia (Sports Medicine Program)

Talking about malnutrition is not always about stunting, wasting, or underweight. Malnutrition covers all conditions caused by not eating enough or too much. According to WHO, malnutrition refers to deficiencies, excesses, or imbalances in an intake of a person's energy and/or nutrients.[1] By looking at this definition, obesity and overweight problems are also considered as malnutrition. It is no longer a secret that obesity is a huge problem in our world right now. When we say that obesity is caused by "eating too much", we might think that it will only happen in developed countries where they have no undernutrition problem. But, is that true? The fact is that obesity is a problem in not only developed countries but also developing countries. How come? The socioeconomic discrepancy in developing countries makes both undernutrition and overnutrition coexist. This is what WHO calls as double burden of malnutrition.[2]

While undernutrition causes many deaths especially in developing countries, obesity and overweight kill a lot more people who are underweight worldwide. Worldwide obesity has tripled since 1975, and in 2016, 39% or more than 1.9 billion adults aged 18 years and older were overweight. Over 650 million of these adults were obese. To make it even worse, over 340 million children and adolescents aged 5-19 were overweight or obese in 2016.[3] A WHO report in 2009 stated that overweight and obesity are the fifth leading risk factor causes of death worldwide with 2.8 million deaths, meanwhile childhood underweight ranked ninth with 2.2 million deaths.[4] Overweight and obesity clearly pose more danger and risk of death than underweight.

The main culprit of obesity is sedentary lifestyle. Although it is true that genetics and some medical conditions play a role in causing obesity, poor diet and lack of physical activity are the biggest contributors. Too much calorie intake and too little physical activity will make calorie surplus and eventually weight gain in a longer term. Weight gain will cause overweight, or even worse, obesity. Too many calories, especially in the form of simple carbohydrates, will cause an insulin spike; and this insulin spike will transform glucose to glycogen which will be stored in the muscle and liver, and to fat which will be stored in adipose tissue to make sure the blood glucose level is in check. Therefore, too much sugar will increase our fat storage as well. Insulin can also penetrate our brain to send signal to hypothalamus when we had enough food already. When exposed to high carbohydrate diet in a long time, an insulin resistance will develop a condition where your cells ignore the signal of insulin in your body to take glucose into your cells while your pancreas keep on producing insulin, resulting in a high blood glucose level, a rise on fat synthesis, and even more weight gain. This condition will increase your risks of metabolic syndrome, heart

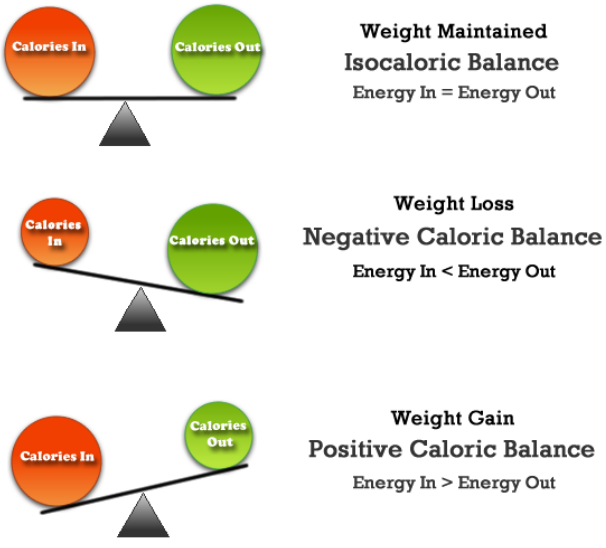


attack, stroke, non-alcoholic fatty liver, and eventually some cancers. Insulin resistance also causes the brain to ignore the signal that we are full.[5]

Besides glucose, eating too much fat, especially trans fat, is also a contributing factor. Fat is actually essential to our body, but eating the right amount and the right type of fat is important to get the health benefits. We must keep in mind that fat has higher caloric content, which is eight calories per gram, compared to carbohydrate and protein, which are four calories per gram. When too much fat is consumed, it will be stored in our adipose tissue. When our adipose tissue is "full", it will release a hormone called leptin that signals our brain to down-regulate our appetite. Distinct from leptin, ghrelin is produced by our stomach to signal hypothalamus that we are hungry. When someone keeps on eating caloric dense food and fails to control appetite, a leptin resistance will emerge. Leptin resistance will make a person tend to overeat or addicted to food. This condition, together with insulin resistance, will heighten the intake of palatable food and further worsen the weight gain.[5]

In our body, fat is stored as subcutaneous fat which sits under the skin and visceral fat which chokes your organs. Compared to subcutaneous fat, visceral is deadlier. Visceral fat also contributes to insulin resistance and both create a never-ending loop that makes the condition even worse.[6] A high visceral fat depot in our gut is also related with systemic inflammation in obese human[7] and play role in inflammatory bowel disease.[8] Visceral fat is related to an increased risk of heart diseases, diabetes, hypertension, stroke, Alzheimer's dementia, and some cancers such as colorectal, breast, prostate, uterine, liver, and kidney. Other complications of obesity that might occur include obstructive sleep apnea, musculoskeletal problems, cholesterol gallstones, infertility, eclampsia in pregnancies, and menstrual disturbances in women.[9]

Body Mass Index (BMI) may be the famous way to measure whether someone is underweight, normal, overweight, or obese. However, BMI is not the real representa-



tion of your body composition.[10] Body composition is one of the health-related fitness components that can be measured by bioelectrical impedance analysis (BIA). BIA will estimate your water, muscle, bone, and fat mass by measuring the ability of biological tissue to impede electric current.[11] Although the gold standard to measure visceral fat is by using CT-Scan or MRI, BIA can be a low-cost alternative to estimate our body's visceral fat rating.[12] This will help a patient to measure and evaluate the progress of their weight management.

In spite of the dangerous consequences of obesity, tackling overweight and obesity is not as easy as you might think. While there are many quick shortcuts offered to the society, they do not always solve the problem. Many herbal and natural pills and weight loss supplements offer no more than just placebo effect. Some surgery procedures such as bariatric surgery and liposuction emerge as a solution for morbid obesity.[5] Many drugs such as lipase inhibitor and "appetite suppressant" are also used to help patient with obesity.[5] However, are we going to rely on drugs and surgery to fight it? The true cores of obesity management are a new lifestyle and mindset. By changing the old habit into a more healthy habit, an obese patient will benefit from it in a long run. A more active routine and healthier diet are compulsory in managing obesity.[5] A proper stress management and sufficient sleep are also needed. If we fail in creating this new mindset and lifestyle, a successful weight loss may be pointless, and a yo-yo effect might happen afterwards. Being in a state of obesity for a long time makes weight loss a hard thing to achieve due to the chronic inflammation and leptin-insulin resistance. There is also a big chance that those who lose weight might become obese again.[5]

The quote "weight loss is 70% diet and 30% exercise" might not be 100% true, but it can be a simple start to fight against obesity. Without a proper diet, exercise will not help that much in weight loss. From what we learned in the explanations above, obesity starts from wrong diet, so the most logical way to start is to fix it. By controlling your calorie intake while increasing the energy expenditures, a weight loss can be achieved.[13] Research shows that no matter what the method of the diet is, either it is Ketogenic, Paleo, intermittent fasting, Mediterranean, or any other type of diet, as long as a caloric deficit is created, a weight loss will be achieved.[5,14] No diet method is superior to the others, so the best diet for you is the one that you can stick with for a long term[14,15], and it should be a balanced one. Yes, it is not easy, and it takes time, but it is better to start now than to regret it later. Remember that the longer we are in the state of obesity, the harder it is to reach a healthy weight. A gradual weight loss is more sustainable than a rapid weight loss. Extreme diet and rapid weight loss could make you sick and are not sustainable because they will not create a long-term healthy habit. You do not need to count precisely every single calorie that you ingest, but awareness is the key. Try swapping unhealthy foods such as fast food, processed food, and sugary drinks, with healthier choices like fruit and vegetables, lean proteins, complex carbohydrates, and limit foods that are high in fat, sugar, and salt. Thus, as the title said that "abs are made in the kitchen", you might start to think of what you put in your mouth and make a wiser food choice to earn a lean and healthy body, and a better quality of life.

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INA-RESPOND Newsletter

Caffeine in My Coffee: My Love, Should I Keep or Let You Go?

By: ALY DIANA

Some of us love the caffeine in our coffee, maybe a little too much. However, we are not alone. Many people, researchers, and scientific communities out there also feel the same. Caffeine is probably the most frequently ingested pharmacologically active substance in the world. A very famous review (Nawrot et al., 2003) about effects of caffeine on human health has been cited 900 times up to today, and >10,000 caffeine-related papers have been published, >5,000 of which address the effects or exposure in humans, and >800 reviews related to various human health effects.

Another systematic review (SR) was conducted to include data published since 2003 and through 2015 to update the review by Nawrot et al. (2003), to determine whether more recent literatures published still support the conclusions that caffeine consumption at certain amount is safe enough. And yes, through those years, the evidence still conclude that consumption of caffeine up to 400 mg/day for healthy adults, 300 mg/day for healthy pregnant women, and 2.5 mg/kg-day for healthy children is not associated with adverse effects.

However, given the voluminous scope, this effort was limited to evaluate potential effects for five main outcomes: (1) acute toxicity (defined herein as abuse, overdose, and potential death), (2) cardiovascular, (3) bone and calcium (with consumption of adequate calcium), (4) behavior, and (5) development and reproductive toxicity. The areas of genotoxicity, mutagenicity, and carcinogenicity were not included. Please be careful that HEALTHY is a very important factor. People with hypertension or other health issues and old people may be more vulnerable to the adverse effects of caffeine.

The consumption of 400 mg/day can roughly translate into the amount of caffeine in four cups of brewed coffee. A cup of coffee, for example, contains 29–176 mg of caffeine depending on its strength. Be careful, caffeine is not only found in coffee, but also found in other common beverages (tea, soft drinks, energy drinks), in products containing cocoa or chocolate, and in medications. Caffeine concentrations in white, green, and black teas ranged from 14 to 61 mg per cup. So if we are a coffee and a tea and a chocolate lover, we might have to choose.

An extra note, many studies have also explored the benefits of coffee consumption (not caffeine!) on the reduction or protection of diseases. Although some of the studies showed promising results, robust randomised controlled trials are still needed to understand whether the observed associations are causal.

Oh well, for now, let's sit back and relax, and enjoy our coffee! Please make sure that we are healthy before taking a sip.

Take home message: Well done systematic reviews, with or without an included meta-analysis, are commonly considered to provide the best evidence for all question types as they are based on the findings of multiple studies that were identified in comprehensive, systematic literature searches. However, the position of systematic reviews at the top of the evidence hierarchy is not absolute. For example: (1) The process of a rigorous systematic review can take years to complete, and findings can therefore be superseded by more recent evidence; (2) The methodological strengths and limitations must be appraised by the reader before being applied; (3) A large, well conducted Randomised Controlled Trial (RCT) may provide more convincing evidence than a systematic review of smaller RCTs.

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INA-RESPOND Newsletter

HIV/AIDS Workshop at Double Tree Hotel by Hilton, Jakarta

EVENT

Indonesia Research Partnership on Infectious Diseases (INA-RESPOND) is a clinical research collaboration on infectious diseases between the National Institute of Health Research and Development (NIHRD), Ministry of Health of Indonesia and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). We establish a network of infectious diseases research and build capacity and infrastructure to conduct high quality clinical research in Indonesia. Established in 2011, we have completed a study to determine the etiology of acute fever in hospitalized patients (the Etiology of Acute Febrile Illnesses Requiring Hospitalization / AFIRE Study). Our ongoing studies include a 2-year cohort on drug-resistant tuberculosis (Tuberculosis Research on Drug Resistance / TRIPOD Study) and a 3-year cohort on HIV infection (Prospective Observational Cohort on HIV Infection and Risk-Related Coinfections/ Comorbidities in Indonesia / INA-PROACTIVE).

With regards to the vision of Three Zeros (zero AIDS-related deaths, zero new HIV infections, and zero HIV/AIDS stigma and discrimination), the HIV/AIDS epidemic in Indonesia is unfortunately still increasing, as opposed to other neighbouring countries such as India and Thailand. The estimated HIV prevalence rate in Indonesian adults aged 15-49 years rose from 0.3% in 2011 to 0.5% in 2015. Indonesia, India, and China account for 78% of new HIV infections in Asia Pacific region in 2014. In 2016, there was an estimated 622,435 people living with HIV (PLWH) in Indonesia; 248,250 of the PLWH knew their HIV statuses and 79,833 of them were on treatment. The HIV transmission pattern had moved from injecting drug use (53% in 2001-2005 to 34% in 2011) to heterosexual transmission (37% to 71% during that same period).

The INA-PROACTIVE study is aimed to fill the gap on viral suppression among PLWH in Indonesia. In addition, we want to capture HIV disease progression and outcomes, as well as its association with various demographical and clinical factors. Between January and September 2018, INA-PROACTIVE study has enrolled over 850 participants from 12 sites in Indonesia. The 12 sites are either type A or B or private hospitals capable of delivering HIV care, which include Dr. Cipto Mangunkusumo Hospital, Persahabatan Hospital, and St. Carolus Hospital in Jakarta; Dr. Kariadi Hospital, Semarang; Dr. Sardjito Hospital, Yogyakarta; Dr. Soetomo Hospital, Surabaya; Dr. Wahidin Sudirohusodo Hospital, Makassar; Tangerang District Hospital, Banten; Dr. Adam Malik Hospital, Medan; Budi Kemuliaan Hospital, Batam; Dr. Ansari Saleh Hospital, Banjarmasin; and Dr. A. W. Sjahranie, Samarinda. Although the study site team has been given training prior to site activation, it is deemed necessary to refresh their knowledge in managing HIV patients, from making diagnoses and providing treatment of HIV infection and its coinfections/comorbidities, as well as addressing social implications of PLWH.

Objective

The objectives of the INA-RESPOND HIV seminar are to:

- Refresh knowledge on HIV basics, such as epidemiology, retrovirology, diagnostics and antiretroviral treatment guideline.
- Refresh knowledge on the management of HIV coinfections and comorbidities, such as opportunistic infections, metabolic diseases, cancer, etc.
- Refresh knowledge on the management of pediatric HIV.
- Discuss difficult and interesting cases found in HIV clinic.
- Provide latest update on HIV prevention and challenges.

Agenda and other details can be seen from the leaflet link: HIV Seminar at Double Tree Hotel Jakarta

Looking forward to seeing you in the seminar!

Double Tree Hotel by Hilton, Jakarta

5-7 DEC 2018

HIV/AIDS WORKSHOP

IDI Accreditation

In commemoration of
National Health Day
& World AIDS Day

"35 Years of HIV/AIDS Epidemic: Diagnosis & Treatment of HIV, Co-infections & Co-Morbidities"

Foreign Speakers

Alice Pau, PharmD
Clinical Staff Scientist, NIAID - NIH

Emmanuelle Papot, M.D.
Therapeutic and Vaccine Research Institute, Kirby Institute, UNSW Sydney

Frank Maldarelli, M.D., Ph.D.
National Cancer Institute, NIH

H. Clifford Lane, M.D.
Deputy Director for Clinical Research and Special Projects, NIAID

Henry Masur, M.D.
Critical Care Medicine Dept, Clinical Center, NIH

JoAnn Mican, M.D.
CAPT, USPHS Staff Clinician, ICMOB, DCR, NIAID - NIH

Mark Polizzotto, M.D.
Therapeutic and Vaccine Research Institute, Kirby Institute, UNSW Sydney

Indonesian Speakers

Dr. Darma Imran, Sp.S
Dept. Neurologi, RSCM

Dr. dr. Evy Yunihastuti, Sp.PD-KAI
Dept. Medik Penyakit Dalam, RSCM

Evi Sukmaningrum, M.Si., Ph.D
Direktur Pusat Penelitian AIDS, Unika Atmajaya, Jakarta

Dr. Imran Pambudi, MPHM
KaSubdit Tuberkulosis, Ditjen P2P, Kemenkes RI

Dr. Nia Kurniati, Sp.A-KAI
Dept. Medik Ilmu Kesehatan Anak, RSCM

Prof. Dr. dr. Retno Wahyuningsih, MS, SpParK
Divisi Mikologi, Dept. Parasitologi Klinik, FKUI

Dr. Rudi Wisaksana, SpPD, KPTI
Dept. Penyakit Dalam, RSHS

Prof. Dr. dr. Tuti Parwati Merati, Sp.PD-KPTI
Dept. Penyakit Dalam, RS Sanglah

Registration fee:

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INA-RESPOND Secretariat, Gedung Labdu Lantai 5 Badan Litbangkes - Jakarta Indonesia

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INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASES

INA-RESPOND Newsletter

The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

The INA-RESPOND newsletter welcomes all network members and stakeholders to contribute by submitting articles related to the network's studies and interests. Send your articles or subscribe to our latest newsletter by sending an email to INA.Secretariat@ina-respond.net