# INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

September 2019

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NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2019

# INA-RESPOND newsletter

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FEATURES

INA-RESPOND Newsletter

# TRIPOD & INA-PROACTIVE Study Updates

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

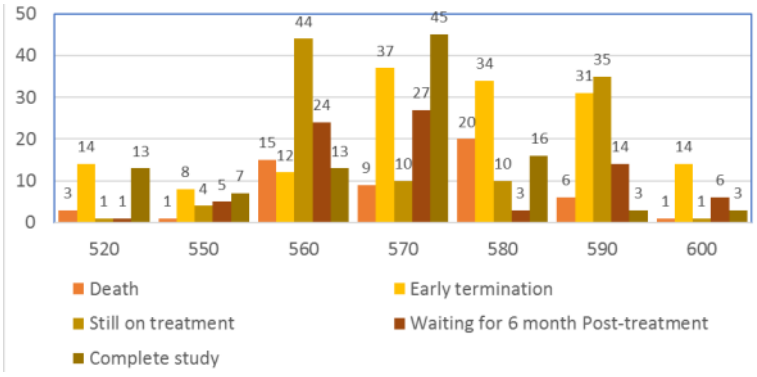


*Figure 1.Participant status per site based on uploaded CRF per 31 August 2019*

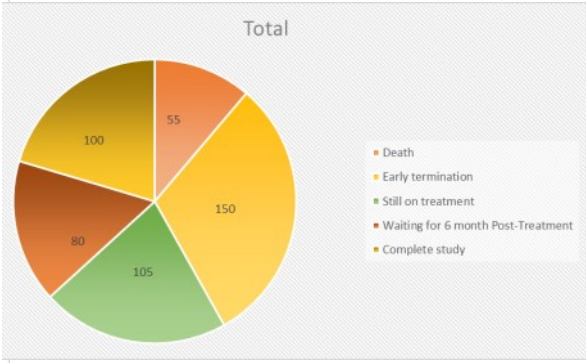


*Figure 2. Total Participants Status based on uploaded CRF per 31 August 2019*

## INA102

### PARTICIPANT STATUS

Per 31 August 2019, the total ongoing participants in TRIPOD study are 185 out of 490 enrolled participants. From the 185 current participants, 105 are still on TB treatment while 80 are waiting for 6-month post-treatment visit. One hundred participants have completed the study while 205 participants are terminated early (including death). Therefore, there are still 37.8 % participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are 2 participants from site 520 (RS Sanglah Denpasar) who still need to be followed up, 9 participants from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 68 participants from site 560 (RSUP dr. Kariadi Semarang), 37 participants from site 570 (RSUD dr. Soetomo Surabaya), 13 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 49 participants from site 590 (RSUP Persahabatan Jakarta), and seven participants from site 600 (RSUP dr. Adam Malik Medan).

Result for baseline culture and DST from all sites are not complete yet. The five sites that have all the full results for culture and DST are site 520, site 550, 570, 580, and site 600.

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

*Figure 3.Culture and DST results up to 30 June 2019*

## INA104

INA-RESPOND network had its second Network Steering Committee of 2019 on Aug 19, 2019. After INA104 presentation and discussion, and based on subject representativeness analysis; the committee agreed that the projection of enrolled subjects had represented the HIV patient population receiving treatment at each site. Therefore, the Steering Committee decided to stop the study enrollment at study sites at four different points (Aug 31, Sept 30, Dec 31, 2019 and Jun 30, 2020). The enrollment stop (four months earlier) is staggered to maximize data quality and subject retention during follow up period. The enrollment stop schedule can be seen in the table on the right.

As of Sep 11, a total of 3,580 subjects had been enrolled consisting of 3,427 adults and 153 paediatrics, from a total of 6,120 subjects screened. The enrollment rate was 58.49% from total screening. Details are shown in Figure 2. The enrollment failure rate was 41.50% from total screening, details on reasons for failure are shown in Figure 3.

The following site visits for INA-PROACTIVE study have been conducted in the last month. The details are:

1. 3rd Site Monitoring Visit to RSUPN Dr Cipto Mangunkusumo, Jakarta on 19 – 22 Aug 2019
2. 1st Site Monitoring Visit to RSUD Dr Soedarso, Pontianak on 26 – 28 Aug 2019
3. 2nd Site Monitoring Visit to RSUD Abdul Wahab Sjahranie, Samarinda on 2 – 5 Sep 2019

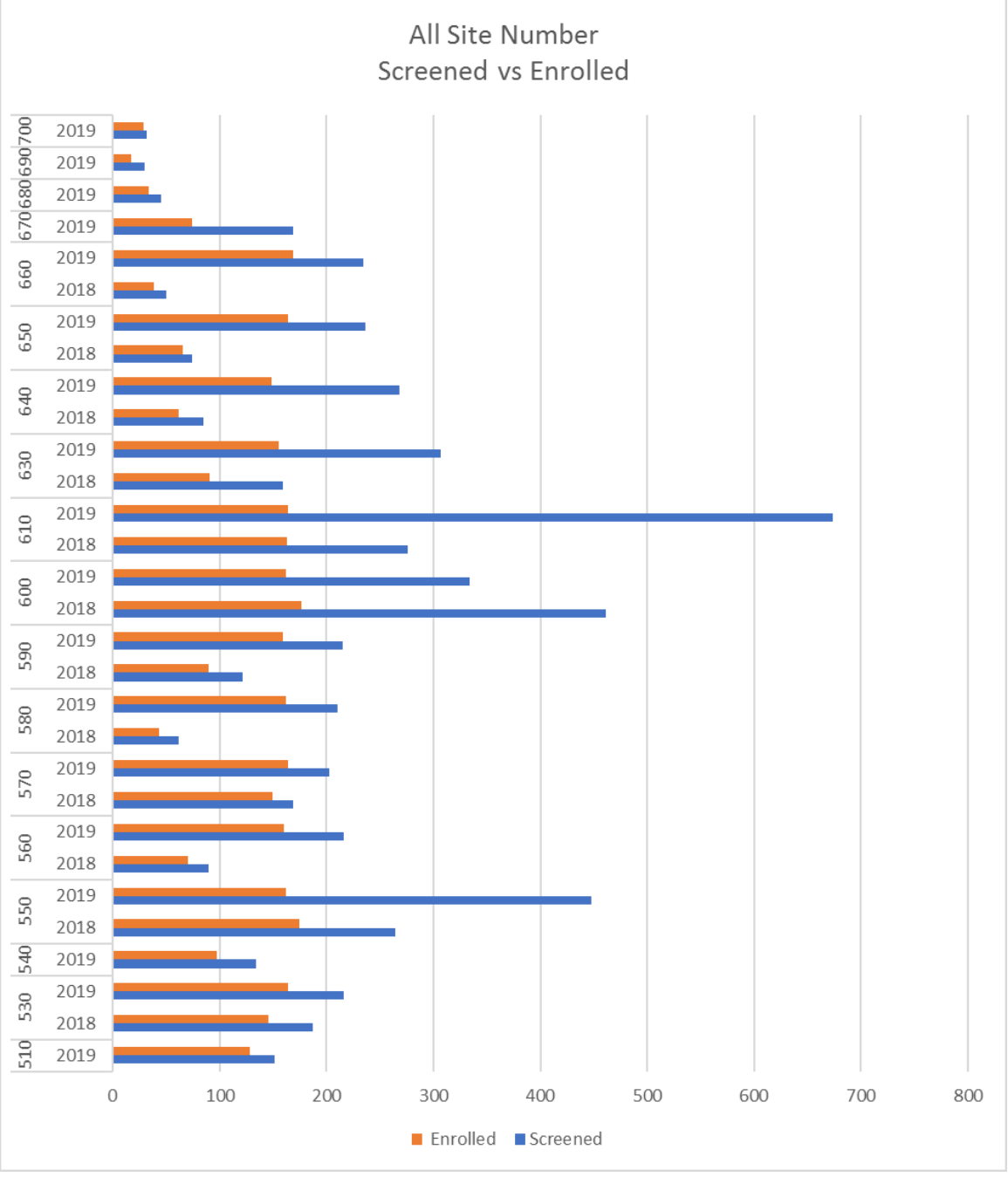


Figure 2

Enrollment rate and number

| Site # | Hospital Name | Date of Enrollment Stop | Projection of Number of Subjects |
|---|---|---|---|
| 600 | Adam Malik | 31-Aug-19 | 332 |
| 610 | Kabupaten Tangerang | 31-Aug-19 | 323 |
| 550 | Wahidin Soedirohusodo | 31-Aug-19 | 325 |
| 570 | Soetomo | 31-Aug-19 | 312 |
| 530 | Cipto Mangunkusumo | 31-Aug-19 | 306 |
| 630 | Ansari Saleh | 31-Aug-19 | 255 |
| 590 | Persahabatan | 31-Aug-19 | 245 |
| 650 | Budi Kemuliaan Batam | 31-Aug-19 | 226 |
| 560 | Kariadi | 31-Aug-19 | 225 |
| 640 | St. Carolus | 30-Sep-19 | 225 |
| 660 | A.W. Sjahranie | 30-Sep-19 | 221 |
| 580 | Sardjito | 30-Sep-19 | 220 |
| 510 | Hasan Sadikin | 31-Dec-19 | 208 |
| 540 | Sulianto Saroso | 31-Dec-19 | 177 |
| 670 | Zainoel Abidin | 31-Dec-19 | 163 |
| 680 | Soedarso | 31-Dec-19 | 120 |
| 700 | T.C. Hillers | 30-Jun-20 | 198 |
| 690 | Abepura | 30-Jun-20 | 151 |
| | **Total** | | **4,232** |

| Reason for failures | 510 | 530 | 540 | 550 | 560 | 570 | 580 | 590 | 600 | 610 | 630 | 640 | 650 | 660 | 670 | 680 | 690 | 700 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Suspect HIV | 1 | 0 | 0 | 16 | 0 | 0 | 0 | 0 | 2 | 11 | 11 | 0 | 0 | 8 | 14 | 0 | 0 | 0 | 63 |
| 2. Refuse to consent | 4 | 13 | 3 | 6 | 11 | 0 | 1 | 7 | 4 | 5 | 0 | 1 | 9 | 3 | 3 | 0 | 0 | 0 | 70 |
| 3. Unwilling to comply with the study procedures | 0 | 25 | 4 | 2 | 18 | 4 | 10 | 0 | 28 | 28 | 0 | 17 | 6 | 2 | 0 | 0 | 5 | 0 | 149 |
| 4. Plans to move away | 2 | 11 | 1 | 12 | 7 | 0 | 6 | 8 | 13 | 7 | 14 | 12 | 7 | 3 | 3 | 0 | 5 | 1 | 112 |
| A. No show | 5 | 36 | 18 | 118 | 5 | 16 | 2 | 21 | 364 | 349 | 79 | 27 | 9 | 14 | 29 | 6 | 0 | 0 | 1098 |
| B. Busy (in a hurry) | 1 | 6 | 7 | 39 | 9 | 15 | 10 | 5 | 15 | 35 | 6 | 72 | 28 | 28 | 10 | 4 | 1 | 1 | 292 |
| C. Has been enrolled | 10 | 0 | 3 | 168 | 26 | 21 | 10 | 44 | 30 | 162 | 104 | 14 | 21 | 19 | 35 | 1 | 1 | 1 | 670 |
| D. Participated in other CT | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 |
| E. Hospitalized or unwell | 0 | 0 | 0 | 13 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 19 |
| F. Others (e.g. no referral letter from other health facility, equipment trouble) | 0 | 2 | 1 | 1 | 0 | 3 | 8 | 0 | 1 | 24 | 6 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 47 |
| **Grand Total** | **23** | **93** | **37** | **375** | **76** | **59** | **67** | **87** | **457** | **623** | **220** | **143** | **81** | **77** | **95** | **11** | **13** | **3** | 2540 |

**Figure 3. Reason for Failures**

INA-RESPOND Newsletter

# OCCULT HEPATITIS B INFECTION, AND THE IMPORTANCE OF HBV CO-INFECTION HIV

By: dr. Yan Mardian



Congratulations to Dr. Yan Mardian for completing his Ph.D course at Kobe University, Japan. Dr. Yan Mardian is a former Research Assistant of AFIRE Study from May 01, 2014 to August 15, 2015. During the employment period, dr. Yan had contributed to enrollment of acute febrile patients from Dr. Sardjito Hospital – Faculty of Medicine Universitas Gadjah Mada (UGM), or site 580. After one year gaining research skill and experience, he decided to resign from INA-RESPOND in 2015 to pursue a Ph.D. course at Kobe University, Japan, which is one of the oldest and largest national universities in the country. It is also one of the highest-ranking national universities in Japan that had attracted more than 1300 international students. He was enrolled as a Ph.D. student under the supervision of Prof. Yoshitake Hayashi, MD, Ph.D. (Anatomy Pathologist) and Yoshihiko Yano, MD, Ph.D. (Internist-Hepatologist) in Division of Infectious Disease Pathology, Kobe University Graduate School of Medicine.


His principal works were doing molecular and genetic research of hepatitis B virus (HBV) and also conducting international collaboration in HBV and hepatocellular carcinoma (HCC) study. During his study, he had collaboration with Faculty of Medicine UGM, in specific to analyze samples from Dr. Sardjito Hospital for HBV genome characteristic obtained from blood donor population, chronic patients and hepatocellular carcinoma (HCC) patients, and also performed cohort-survival study for non-invasive Abdominal CT Scan body composition data in predicting the outcome of HCC patients.

During his four-year study period, he also had opportunities to present his works in local and international forums. At least eight seminars he had participated as an oral or poster speaker. From those conferences, he received best poster presentation award in The Asian Pacific Association for the Study of the Liver/ APASL (Beijing, 2016), Young Investigator Award (YIA) in the 4th Shinryoukai Award Meeting (Kobe, 2016), and travel grant award in International Digestive Disease Forum/IDDF (Hong Kong, 2018).

In July 2019, he completed dissertation thesis examination titled "Genetic polymorphisms of HLA-DP and isolated anti-HBc are important subsets of occult hepatitis B infection in Indonesian blood donors: a case-control study" that had been previously published in Virology Journal. In this paper, he studied about Occult hepatitis B infection (OBI), defined as the presence of hepatitis B virus (HBV) DNA on hepatitis B surface antigen (HBsAg)-negative individuals. He enrolled blood donor subjects from Dr. Sardjito Hospital and doing molecular analysis to detect OBI and its correlation with HBV specific antibodies (anti-HBc and anti-HBs) and HLA-DP single nucleotide polymorphisms (SNPs). Here, he provides novel insight that HLA-DP variants were associated with OBI detection in seropositive donors. The minor allele of rs3077 (T) in the HLA-DPA1 gene was related to an increased risk of OBI presence. A combination of haplotype markers (TGA for rs3077–rs3135021–rs9277535) was also associated with OBI detection. This study also indicated that HBV isolated anti-HBc, which refers to the presence of anti-HBc antibody without anti-HBs, has a significant role in predicting latent HBV infection. The results suggest that the combination of SNP genotyping in the HLA-DP gene and HBV serological marker testing, especially anti-HBc, may prevent OBI transmission. As note that in Indonesia, HBsAg remains the only serological marker tested in a routine blood donor to detect HBV, despite its endemicity for HBV infection.

Although had being recognized since the 70s, general interest in OBI just arose and became a significant issue of hepatology research from 1999, when a study published in The New England Journal of Medicine revealed an extensive series of HBsAg-negative patients with chronic liver disease (CLD), were positive for HBV genomes by testing the liver biopsy specimens. That study highlighted the clinical importance of OBI, which may favor or accelerate the progression toward cirrhosis of hepatitis C virus (HCV)-related chronic hepatitis, and also new perspective towards virological aspects that OBI viruses usually have no genetic mutations capable of preventing viral replication as well as HBsAg synthesis. Although it appears that in the vast majority


of cases, OBI does not lead to any clinical sequelae/ implications, however, OBI may result in the transmission of HBV infection to blood or organ transplant recipients, and reactivation of HBV replication in patients receiving cancer chemotherapy or other immunosuppressive therapies. There is a resurgence of interest in occult hepatitis B because of the widespread use of potent B cell-depleting monoclonal antibodies against CD20, such as rituximab (and anti-CD52). These agents are associated with severe, sometimes fatal HBV reactivation in patients with occult HBV infection up to 12 months after cessation of rituximab therapy. It is, therefore, essential to monitor the HBV DNA levels in these patients and initiate antiviral therapy once HBV DNA levels become detectable.

Indonesia has the third-highest prevalence of HBV infection worldwide, with a moderate to the high prevalence rate, ranges from 2.1% to 10.5%, that affects its 242 million people. The prevalence rate of OBI may vary between the high-risk group and low-risk group. In the low-risk group, such as healthy blood donor, endemicity of HBV infection correlates with the prevalence of OBI. However, in a high-risk group, such as Chronic HCV, HIV, and HCC subjects, the prevalence of OBI may increase up to more than 50% of those population. There are an estimated 400 million people worldwide with chronic hepatitis B virus (HBV) infection, and an estimated 40 million people are infected with HIV. Co-infection with HBV and HIV is common because of shared blood-borne transmission routes, particularly injection drug use (IDU), with estimates for the prevalence of co-infection ranging 4–23%. A previous study in 2012 showed that HBV co-infection, including occult HBV infection, was common in HIV patients in Surabaya, East Java, Indonesia. Overall, 15.3% (18/118) of the patients were hepatitis B surface antigen (HBsAg) positive, whereas 27.1% (32/118) were HBsAg negative HBV DNA positive, or having occult HBV infection observed in that study. It was noteworthy that Indonesia had shown a rapid epidemic growth of HIV, and the estimated number of people with HIV had increased approximately 32-fold from 12,000 in 2001 to 380,000 in 2011.

Highly active antiretroviral therapy is used to treat patients worldwide, and HIV is now well controlled in many countries. However, viral hepatitis caused by HBV and liver toxicity caused by HAART are issues for patients with HBV and HIV co-infection undergoing HAART therapy. The NRTIs lamivudine (LMV), emtricitabine (FTC) and tenofovir (disoproxil fumarate (TDF) and alafenamide (TAF)) all have dual activity against both HIV and HBV. Notably, Lamivudine frequently induces multidrug resistance in the RT domain of the polymerase region of HBV. M204I and L180M are common amino acid mutations that cause multidrug resistance. The magnitude of the HBV drug resistance in HIV patients also had not been extensively studied in Indonesia.

The clinical significance of occult HBV infection in HIV-infected patients is still controversial. However, even with effective suppression of both HIV and HBV replication, morbidity and mortality are significantly higher in those with HIV-HBV co-infection than with HIV alone. There is an approximately five-to six-fold risk increase in HCC incidence amongst HIV-infected individuals compared with the general population, and this increased risk has persisted with ART. However, the mechanism of how HIV infection accelerates the progression of HBV-related liver disease, particularly in the presence of HBV-active ART still needs to be elucidated.

In conclusion, considering the rapid increase of HIV infection and HBV endemicity in Indonesia, a large and multicenter study is needed to estimate the burden of overt and occult HBV co-infection in Indonesia blood donor. Also, molecular studies should be conducted to understand the interaction between these two chronic viral infections better. Moreover, clinicians and health workers should consider the national guidelines for prophylaxis, screening, and treatment of HBV-coinfection in Indonesian HIV patients.

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INA-RESPOND Newsletter

# MYERS–BRIGGS TYPE INDICATOR® (MBTI®)

By: Aly Diana

The Myers-Briggs Type Indicator® (MBTI®) has been very popular and widely used. It is an 'old' personality inventory, invented a long time ago. The theory was introduced by Carl G. Jung in 1920s, and the MTBI was initially developed in 1940s by Katherine Cook Briggs and Isabel Briggs Myers. The essence of the 'psychological types' theory is that much seemingly random variation in the behavior is quite orderly and consistent, being due to fundamental differences in the ways individuals prefer to use their perception and judgment. Millions of people worldwide have taken the Indicator each year since its first publication in 1962.

Although the website (https://www.myersbriggs.org/my-mbti-personality-type/mbti-basics/) has claimed that hundreds of studies over the past 40 years have proven the instrument to be both valid (it measures what it says it does) and reliable (produces the same results when given more than once), other studies have shown mixed results. Therefore, it is essential to understand the ability of these tools. The tools will help the identification of basic preferences of each of the four dichotomies specified or implicit in Jung's theory (which will be mentioned shortly) and the identification and description of the 16 distinctive personality types that result from the interactions among these preferences. One important thing to remember, the MBTI tool/instrument sorts for preferences and does not measure trait, ability, or character. Type is generally ingrained and does not change over time. However, the strength of our preferences may change as we experienced things in life.

Psychiatrist Carl G. Jung speculated that people experience the world using four principal psychological functions – and that one of these four functions is dominant for a person most of the time. Below are the brief explanations of the four categories in the MTBI:

Favourite world: Do you prefer to focus on the outer world or on your own inner world? This is called Extraversion (E) or Introversion (I); Information: Do you prefer to focus on the basic information you take in or do you prefer to interpret and add meaning? This is called Sensing (S) or Intuition (N); Decisions: When making decisions, do you prefer to first look at logic and consistency or first look at the people and special circumstances? This is called Thinking (T) or Feeling (F); and Structure: In dealing with the outside world, do you prefer to get things decided or do you prefer to stay open to new information and options? This is called Judging (J) or Perceiving (P).

The goal of knowing about personality type is to understand and appreciate differences between people. As all types are equal, there is no best type. When we know our type preferences, we can approach our own work in a manner that best suits our style, including how we manage our time, problem-solving, best approaches for decision making, and dealing with stress. Knowledge of type can help us better understand the culture of the place we work, develop new skills, understand our participation in teams, and cope with change in the workplace. It will also help us to understand preferences of others and not just conclude that they are coming from outer space. In a simple word, hopefully the test can help us to get along better, with ourselves and others.

COMIC CORNER


However, the original MTBI is not free (https://www.mbtionline.com/TaketheMBTI).

There are a lot of online free test using the basic concept of the MTBI (for example https://www.16personalities.com/free-personality-test), but we need to recognize that the results are probably not as accurate. And again, we need to acknowledge that this test/indicator only shows our preferences; it is a tool to help and nothing more. So, if we don't think that it will help us, just forget about it. Have fun trying!

References:

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INA-RESPOND Newsletter

# HIV RESISTANCE TESTING

By: Dr. Chuen-Yen Corey-Lau

**Why do we do HIV resistance testing?**

HIV can rapidly become resistant to the antiretroviral medications (ARV) that we use to treat it. Treatment is considered effective when the HIV levels in the blood are undetectable with a standard clinical assay; this is known as viral suppression. If HIV is resistant to a medication, it will not be suppressed by that medication and the viral load will be elevated. Elevated viral loads are associated with worse symptoms, disease progression and transmission.

Resistance testing shows which drugs are no longer effective or are only partially effective. Resistance testing usually entails sequencing techniques that identify specific mutations in the virus, though phenotypic methods that measure the ability of specific drugs to inhibit viral replication can also be used. If mutations cause HIV to be resistant to one ARV, that virus may have mutations that cause it to also be resistant to other ARVs in the same class. This is known as cross-resistance.

HIV resistance testing is very useful when making decisions about an HIV infected person's ARV regimen. It is often done prior to a person starting HIV treatment and when the virus in someone on treatment is not fully suppressed. Based on the resistance testing results and patient characteristics, we can choose the right ARV regimen.

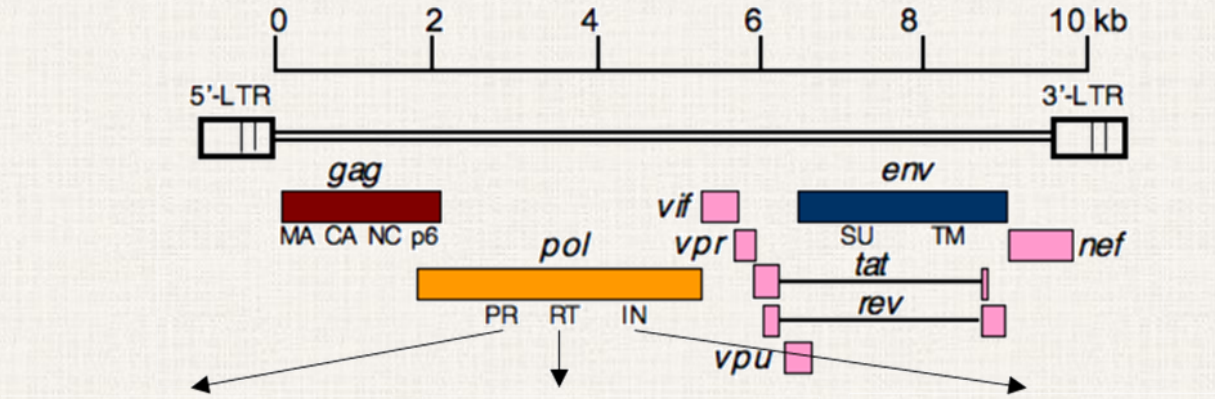
**What's the difference between a genotype and a phenotype?**

There are two general categories of HIV resistance testing – Genotyping and Phenotyping. Genotyping detects the presence of specific mutations in the parts of the HIV genome that code for places where ARV acts. A genotype report gives you a readout of specific mutations with an interpretation that says how susceptible the virus is to available ARVs. This interpretation is based on computer algorithms, not on actual observation of replication in the presence of the drug. On the other hand, phenotyping measures the ability of ARV to inhibit viral replication in vitro. It relies on actual observation of replication in the presence and absence of specific ARVs. A phenotype report tells you how well the patient's virus grows compared to a reference virus in the presence of specific drugs.

We typically start with genotyping. Genotyping is highly reliable for most patients and much easier to perform. It works very well in patients with higher viral loads and when the mutations are in at least 20% of the viral population. Thus genotyping should be performed in treated patients while the patient is still on ARVs or very soon after they have been stopped. If the patient is no longer on the ARV regimen, there will be no selective pressure on the virus and wild-type populations will take over, making it difficult to detect culprit mutations.

**Dr. Chuen-Yen Corey Lau**

National Institute of Allergy and Infectious Diseases (NIAID)




**Major Protease Inhibitor (PI) Resistance Mutations**

| | 32 | 46 | 47 | 48 | 50 | 54 | 76 | 82 | 84 | 88 | 90 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cons | V | M | I | G | I | I | L | V | I | N | L |
| ATV/r | I | IL | V | **VM** | **L** | VTALM | | ATFS | **V** | **S** | **M** |
| DRV/r | **I** | | VA | | **V** | **LM** | **V** | F | **V** | | |
| LPV/r | **I** | IL | **VA** | VM | **V** | **VTALM** | **V** | **AFTS** | **V** | | M |

**Major Nucleoside RT Inhibitor (NRTI) Resistance Mutations**

| | Non-TAMs | | | | | TAMs | | | | | | MDR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 184 | 65 | 70 | 74 | 115 | 41 | 67 | 70 | 210 | 215 | 219 | 69 | 151 |
| Cons | M | K | K | L | Y | M | D | K | L | T | K | T | Q |
| 3TC | **VI** | **R** | | | | | | | | | | **Ins** | **M** |
| FTC | **VI** | **R** | | | | | | | | | | **Ins** | **M** |
| ABC | VI | **R** | E | **VI** | **F** | L | | | W | FY | | **Ins** | **M** |
| TDF | *** | **R** | E | | F | L | | R | W | FY | | **Ins** | **M** |
| ZDV | *** | *** | * | * | | **L** | **N** | **R** | **W** | **FY** | QE | **Ins** | **M** |

**Major Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations**

| | 100 | 101 | 103 | 106 | 181 | 188 | 190 | 230 |
|---|---|---|---|---|---|---|---|---|
| Cons | L | K | K | V | Y | Y | G | M |
| DOR | I | EP | | **AMI** | CIV | **LCH** | **SE** | **L** |
| EFV | **I** | **EP** | **NS** | **AM** | CIV | **LCH** | **ASEQ** | **L** |
| ETR | **I** | **EP** | | | **CIV** | L | ASEQ | **L** |
| RPV | **I** | **EP** | | | **CIV** | **L** | ASEQ | **L** |
| NVP | **I** | **EP** | **NS** | **AM** | **CIV** | **LCH** | **ASEQ** | **L** |

**Major Integrase Inhibitor (INSTI) Resistance Mutations**

| | 66 | 92 | 118 | 138 | 140 | 143 | 147 | 148 | 155 | 263 |
|---|---|---|---|---|---|---|---|---|---|---|
| Cons | T | E | G | E | G | Y | S | Q | N | R |
| BIC | K | Q | **R** | KAT | SAC | | | **HRK** | H | K |
| DTG | K | Q | **R** | KAT | SAC | | | **HRK** | H | **K** |
| EVG | **AIK** | **Q** | **R** | **KAT** | **SAC** | | **G** | **HRK** | **H** | **K** |
| RAL | AI**K** | **Q** | **R** | **KAT** | **SAC** | **RC** | | **HRK** | **H** | K |

Waheed and Freed. *Viruses*, 2010, *2*, 1146-1180.
Stanford HIVDB. https://hivdb.stanford.edu/.

**Figure 1**: HIV-1 genome with example mutations to commonly used antiretroviral drugs. Note that protease (PR), reverse transcriptase (RT) and integrase (IN) are all on the pol gene. In the mutation tables, the top row shows the amino acid position, the 2nd row shows the code for the wild type reference amino acid, and the rows following each drug abbreviation show the code for the mutated amino acid found in the sequence. Codes shown in bold indicate higher levels of resistance. For example, the mutation K65R codes for high level resistance to tenofovir disoproxil fumarate (TDF).

For highly treatment experienced patients, especially those who have failed multiple ARV regimens, we can add phenotyping. This is helpful when there may be multiple confusing mutations and we are very limited with ARV options. As with genotyping, it is best to do phenotyping while a patient is still on their ARV regimen.

**What is archived resistance and why does it matter?**

Circulating virus in the plasma can be different from the proviral DNA that is archived in infected cells. The archived proviral DNA may have mutations that are only expressed in circulating virus when pressure from the ARV regimen is removed. Since these mutations lead to resistance when expressed, they should be considered when selecting a patient's ARV regimen. Otherwise a patient may be placed on a regimen for which their virus only appears to be sensitive. However, over time the viral load will rise with the inadequate regimen and additional resistance may emerge, which further limits ARV options.

Mutations in the archived proviral DNA that are different from those in the circulating virus will not be detected by normal genotyping or phenotyping, which only analyze circulating virus. Next generation sequencing techniques can be used to identify mutations in the proviral DNA. These mutations can be interpreted with the genotyping algorithms to determine sensitivity to different ARVs.

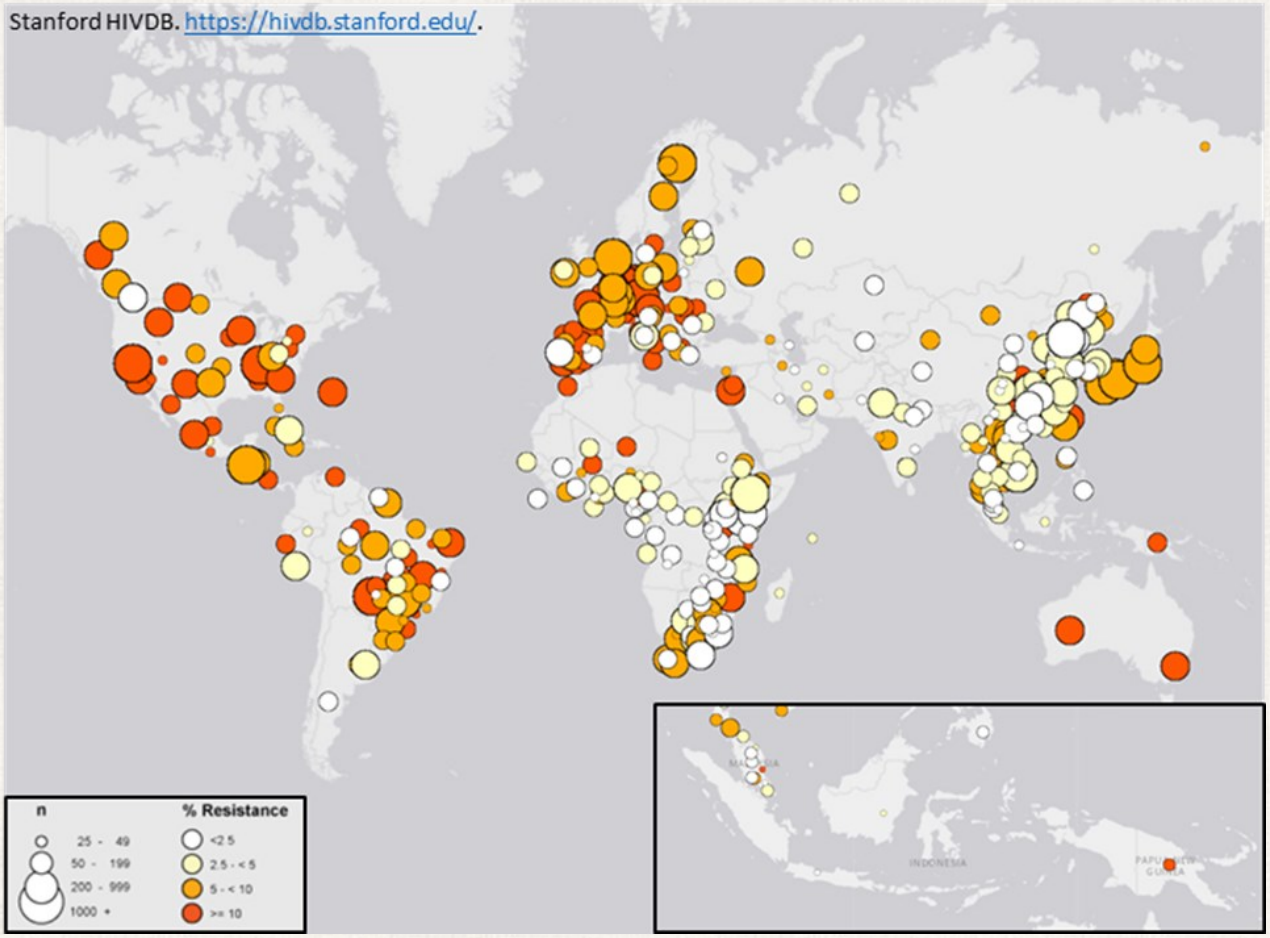



**Figure 2**: Map of worldwide HIV-1 drug resistance in antiretroviral naïve populations. Circle size indicates n contributing to the estimates, color indicates percent resistance. Note the paucity of data for Indonesia, which is shown in the inset.

We look for archived resistance when switching ARV regimens in treatment experienced patients who have no prior resistance data available or when viral load is very low. It should be noted that all mutations that have ever been detected for a particular patient should be considered in determining their ARV regimen.

**What is tropism and when do we test for it?**

HIV uses the CD4 receptor and a coreceptor to enter CD4 T-cells. The coreceptor is either CCR5 or CXCR4. We refer to this as R5 (for CCR5) or X4 (for CXCR4) tropism. Most transmitted viruses are R5, with X4 viruses emerging later. Both R5 and X4 viruses can be present simultaneously. Testing for tropism should only be done when you want to treat with a CCR5 antagonist or when someone has virologic failure on it. Tropism can be determined by both genotypic and phenotypic testing, but we usually do phenotyping.

**How is INA-Respond using resistance testing?**

HIV resistance testing will be implemented for Proactive and DEFT. Genotyping will be performed on specimens with elevated viral loads in the INA-Respond lab using newly installed sequencing machines. These genotype results will help us understand which mutations are prevalent in Indonesia, providing information that public health authorities can use to decide which ARVs to make available in Indonesia. Doing genotyping as part of Proactive and DEFT will also enhance the capacity to incorporate resistance testing into routine clinical care, allowing selection of ARV regimens most likely to achieve viral suppression for individual patients. Thus, HIV resistance testing results from INA-Respond studies can help optimize management of HIV in Indonesia and contribute to control of the epidemic.

INA-RESPOND Newsletter

# CARDIOVASCULAR DISEASE: A HIDDEN THREAT

By: dr. Caleb Leonardo Halim



The heart is one small 'machine' that shapes like a heart and resides inside our chest cavity. This machine's average size is about a fist of an adult and can pump 7,560 liters of blood every day. The heart also beats for 115.000 times a day and up to three billion heartbeats in an average lifetime. A woman's heart beats slightly faster than a man's heart. The human heart weighs less than 500 grams. However, a man's heart, on average, is 50 grams heavier than a woman's heart. This amazing pumping machine is responsible for keeping a human alive by freshly supplying the body with oxygen and nutrients.

Unfortunately, this fantastic little pumping machine does not get enough attention from us. We underestimate its existence by living our life unhealthily. When we eat, we tend to choose fast food. Sadly, most of the time, it's junk food! We are more likely to have a meal that has rich flavor in our mouths, a meal that contains a high level of salt or sugar. Most of us spend our time in our workplace by sitting in front of our desk for a long time without moving around to take a break (see October Newsletter about sitting disease). Also, we work long hours and use this as an excuse, not to exercise or workout. We become more and more physically inactive.

Physical inactivity will make our heart weaker over time, and cholesterol from our unhealthy food is clogging our blood vessels. This condition is terrible for our health; our body is vulnerable to a lot of diseases. One of the most prevalent illness that silently approaches us is cardiovascular disease.

Cardiovascular disease (CVD) along with its friend, stroke, is the number one killer in the world. From 2000, CVD is still the leading cause of death around the world, and its number is getting higher over time. CVD haunts every human being on this planet and will continue to do so unless we break the chain. Unhealthy habits and inactive lifestyle must be eliminated as soon as possible starting from ourselves, our spouse, and children.

According to the American Heart Association (AHA), an excellent healthy lifestyle to keep our hearts happy is to maintaining these few things below, also as known as Life's Simple 7:

**Never/quit smoking.**

Tobacco smoking and all its variants are the second leading risk factor for death in the United States. Overall mortality among smokers in the USA is three times higher compared to non-smokers. One cohort study with more than 500,000 participants (≥60 years old) showed that cardiovascular mortality in smokers is two times higher compared to non-smoker and 1.37 times higher compared to former smoker. Quitting smoking at any age will reduce mortality from smoking-related diseases. The overall risk appears to be the same as nonsmoker after ten years of cessation.

**Keep your Body Mass Index <23**

Body Mass Index (BMI) is a straightforward method to check your overall general health. It's a formula that needs only of your weight and your height.

$$BMI = \frac{\text{Your weight (in kilograms)}}{\text{Your height (in meters)}^2}$$

According to Asia-Pacific guidelines of obesity, we can divide BMI into four categories.

| | Asia-Pacific (BMI) |
|---|---|
| Underweight | <18.5 |
| Normal | 18.5-22.9 |
| Overweight | 23-24.9 |
| Obese | ≥25 |

The goal is to keep your BMI in normal level throughout your life.

**Physically active**

Physical inactivity is the fourth leading risk factor for global death. One study consisting of more than 10,000 participants to record death found that meeting the weekly physical activity requirement reduced all causes of mortality with Hazard Ratio (HR) of 0.64. Adults who did not meet physical activity requirements but were engaged in strength training for ≥ two times a week also benefited from the training, with a 44% lowering adjusted HR of all cause of mortality. Both physical activity and strength training benefit adults in reducing the cause of mortality by 44%-46%.

To stay active, accumulate your weekly activity time into this category: >150 min/wk for moderate intensity or >75 min/

wk for vigorous intensity or >150 min/wk moderate + 2 times vigorous. You can also do strength training 2-3 times a week to add another beneficial effect to your health and overall fitness level and you must reduce your daily sitting time.

A meta analysis study that included more than 1,000,000 participants compared the risk associated with sitting time and television viewing in physically active and inactive study participants. For active participants, sitting was not associated with all cause mortality but watching television ≥5h/day posed higher mortality risk. Inactive participants sitting >8h/day had higher all cause mortality risk than those sitting <4h/day. So, reducing your sitting time and being active are the best ways to keep your heart and life healthy.

**Healthy diet pattern**

Food has always become one of the most important things in our life. It can either bring our body to chaos, causing many diseases or protect our body from many diseases, giving us a better quality of life. It all starts with what we eat today. AHA made some score and list on healthy, balanced diet pattern in AHA Dietary Targets and Healthy Diet Score. You can read it for further details. In 2012, 318,656 (45.4%) cardiometabolic deaths in the United States were associated with the poor dietary pattern. The largest numbers of deaths attributable to diet were estimated to be from high sodium intake (66,508; 9.5% of all cardiometabolic deaths), low consumption of nuts/seeds (59,374; 8.5%), high consumption of processed meats (57,766; 8.2%), low intake of seafood omega-3 fats (54,626; 7.8%), low consumption of vegetables (53,410; 7.6%) and fruits (52,547; 7.5%), and high consumption of sugar-sweetened beverages (51,694; 7.4%). So, be mindful with what goes inside your body because that is where a healthy body emanates.

**Total cholesterol <200 mg/dL**

Cholesterol is one of the primary causal risk factors for atherosclerotic CVD. High cholesterol can be inherited, so it is not only because of what you eat but also genetics. To reduce cholesterol in your body, all you need to do is all previous points that you just read. They'll undoubtedly lower the risk of having high cholesterol. Overweight people are more likely to have high cholesterol, but thin people can be affected as well. A person with any body type can have high cholesterol. People who don't easily gain weight are often less aware of how much saturated and trans fat they eat. Nobody can "eat anything they want" and stay heart-healthy. AHA recommends that all adults >20 years old have their cholesterol checked every four to six year regardless of your weight, physical activity, and diet.

**Blood pressure <120 mm Hg/<80 mm Hg**

High blood pressure is a major risk factor for CVD and stroke. Many factors affect our blood pressure, such as: heredity, race, age, gender, food intake, phycological state, adequate sleep. We need to take all these considerations into account when we talk about blood pressure. Like cholesterol, we can do all the first 4 points to reduce or maintain our blood pressure normal. You can do home blood pressure test by yourself as long as you have the device (sphygmomanometer). Make sure you test everyday at the same time to reduce all other bias errors. Consult to your doctor immediately if you get high measuring test two times in two different occasions.

**Fasting plasma glucose <100 mg/dL**

Not only high blood glucose is one of the primary risk factors for developing CVD and stroke, it is also a primary risk for developing another devastating disease, diabetes mellitus. In 2015, 33.9% of US adults aged ≥18 years had prediabetes, defined as fasting glucose 100 to 125 mg/dL or HbA1c 5.7 to 6.4%. The prevalence HbA1c of prediabetes increased with age and was higher for males (36.6%) than females (29.3%). Low awareness of this disease caused by asymptomatic condition even when someone already in prediabetes states, symptom arise when disease already at diabetes state and that is already too late for our body cause or pancreas cell already heavily damaged. So early screening is important for us all. If you haven't had checked your blood glucose or HbA1c, you should have your blood glucose checked anytime soon. Fasting plasma glucose and HbA1c results according to American Diabetes Association can be seen below:

| Result | Fasting Plasma Glucose (FPG) |
|---|---|
| Normal | <100mg/dL |
| Prediabetes | 100-125mg/dL |
| Diabetes | ≥126mg/dL |

| Result | HbA1c |
|---|---|
| Normal | <5.7 |
| Prediabetes | 5.7-6.4 |
| Diabetes | ≥6.5 |

To have a great and wonderful life would be everyone's dream. To achieve the goal, we need to keep our heart fit and healthy. Start doing all Life's Simple 7, now; start making your heart happy: and have a wonderful life!

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INA-RESPOND website: www.ina-respond.net

# 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