

IN THIS ISSUE

A GLIMMER OF HOPE FOR TUBERCULOSIS TREATMENT

by dr. Retna Mustika Indah.

Before knowing streptomycin, isoniazid, and other famous anti-tuberculosis (TB) drugs, weapons against TB were blunt at best. For over 50 years, doctors treated TB patients at sanatoriums with a regimen of strict rest and fresh air. When long-term results failed to produce, physicians added collapse therapy to the treatment. That invasive procedure, however, resulted in a variety of complications. Past article from early 2000 mentioned pleural calcification with pyogenic empyema and pleural calcification with non-resolvable pneumothorax as the complications of this procedure.

Anti-Tuberculosis drugs are cornerstones of tuberculosis treatment. But, treating TB is not a cakewalk. Since the era of chemotherapy began, resistance to anti-tuberculosis drugs has been a problem. Streptomycin resistance was shortly recognized in 1947 after the introduction of effective anti-TB chemotherapy, but the emergence of Multidrug-resistant tuberculosis (MDR-TB) became widely acknowledged as a global problem after a dramatic outbreak in the early 1990s. After that, resistance to anti-TB drugs is considered as a potentially catastrophic challenge to global public health.

Dr. Anthony S. Fauci in one of his articles wrote that the most critical need for patients with drug-resistant TB is access to new drugs. For many years, scientists have tried to build a better mousetrap on tuberculosis treatment. Ultimately after decades of quiescence in the development of anti-TB medications, we finally have potential multiple new anti-TB drugs, which have novel and unique mechanism of action. **Bedaquiline** and **Delamanid** have been conditionally approved for drug-resistant TB treatment, while other novel compounds such as **PA-284** and **TBA 354** have been evaluated. These newly developed drugs are mainly intended for Drug Resistant TB treatment.

Bedaquiline. For the first time in over 40 years, a new TB drug with a novel mechanism of action is available, and was granted accelerated approval by the United States Food and Drug Administration in December 2012 and by The European Medicines Agency (EMA) in March 2014. This drug actively acts on both actively replicating and dormant mycobacteria by inhibiting the mycobacterial ATP synthase. The clinical evidence showed that adding this diarylquinoline class to a standard background MDR-TB treatment regimen significantly decreased the time to sputum culture conversion and nonsignificantly prevented the acquisition of additional resistance to other accompanying drugs.

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World TB Day is celebrated every year by the health organizations, NGOs, government and non-government organizations including other health agencies to raise the awareness among common public all across the world about the epidemic disease by organizing various campaigns and related activities such as debates on TB prevention and cure, etc. This month, our newsletter features potential TB drugs. What are they? Find the information here!

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Do you know what a biorepository is and how to establish one? This month's newsletter covers brief overview on some of the essential issues in establishing biorepository such as the infrastructure, environment, and approval from study subjects. Moreover, where does our network stand on this issue? And how can we contribute? Read the article and find out for yourself.

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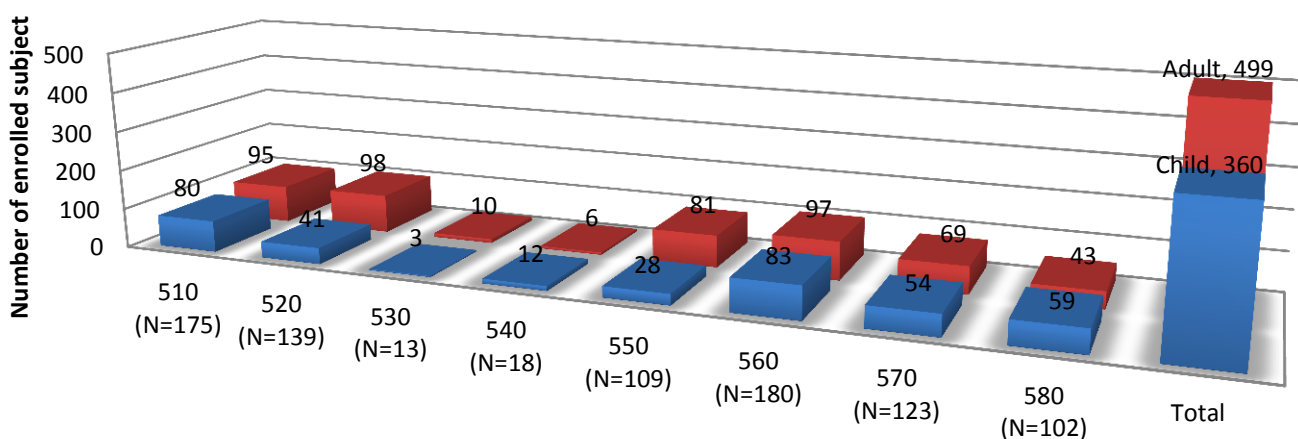
Picture 1 INA-RESPOND Office Warming, NIHRD, Jakarta

Studies' Progress and Updates

by dr. Anandika Pawitri,
 dr. Herman Kosasih,
 dr. Nugroho Harry Susanto,
 dr. Nurhayati,
 dr. Retna Mustika.

AFIRE STUDY

Entering the first week of March in 2015, 2864 patients had been screened. 859 subjects had been enrolled (499 adults and 360 children). Description of screening and enrollment progress can be seen in the chart below:



Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: <https://ina-respond.s-3.com/EdmFile/getfile/797233>

*510– RSUP dr Hasan Sadikin, Bandung
 520 – RSUP Sanglah, Denpasar
 530 – RSUPN dr Cipto Mangunkusumo, Jakarta
 540 – RSPI Prof Dr Sulianti Saroso, Jakarta

550 – RSUP dr Wahidin, Makassar
 560 – RSUP dr Kariadi, Semarang
 570 – RSUD dr Soetomo, Surabaya
 580 – RSUP dr Sardjito, Yogyakarta

For further information on this study, go to <http://www.ina-respond.net/afire-study/>

SEPSIS

Sepsis Study has officially started in Indonesia. Makassar site, RSUP dr. Wahidin Sudirohusodo, started the enrollment on February 26. The enrollment period is until the end of 2015. As for Yogyakarta site, RSUP dr. Sardjito, the Secretariat completed the first Site Preparation (SPV) on March 3-4, and on March 19 – 20 the second SPV will be conducted to cover mostly practical issues in laboratory and how to complete CRF. As the data completion in Sepsis Study is quite different than that in AFIRE study, RA for Sepsis Study has to master not only paper CRF but also electronic CRF.

Jakarta site, RSUPN dr. Cipto Mangunkusumo, is still in the middle of IRB process for protocol submission.

TRIPOD

While waiting for the Implementation Arrangement to be set, the Secretariat continues preparing site 590 (Persahabatan hospital). The subcontract agreement is expected to be signed by The Director of Persahabatan Hospital on the 4th week of March. Upon approval, the secretariat will conduct SPV. The INA102 CRF Completion Guideline version 1.0 and annotated CRF version 1.0 have been approved, and the OpenClinica screen for INA102 is being developed. Data Manager will do the User Acceptance Test after the INA102 OpenClinica screen is ready.

Moreover, site is also preparing the room that will be used for the INA-RESPOND office at site.

Birthdays and Celebrations!

MarCh

- 11 March – **Ms. Eni Yuarni** (National Institute of Health Research and Development / *Badan Litbangkes*)
- 20 March – **Mr. Antonius Pradana**, S.Kom (INA-RESPOND Secretariat)
- 26 March – **dr. Fritzie Cheria** (INA101 Research Assistant at site 510)
- 27 March – **Andi Arahmaniar**, Amd, AK (SEA050 Lab Technician at site 42 – Makassar)
- 28 March – **dr. Tri Wibawa** Ph.D (INA101 Site PI at Site 580)

On this occasion, we would like to express our sincere gratitude for **dr. Irma Susan** (INA101 Research Assistant at site 510) who has left her post. Thank you for your time and dedication to the INA-RESPOND network.



ReDefine STUDY

Under this study, INA-RESPOND is involved in the study initiation visit, study monitoring, and DSMB. The site started screening in December 2014 and as of February 27 a total of 13 subjects was enrolled and 3 SAEs occurred.

The 3 SAEs cases were reported to the local EC and the DSMB Chair and members immediately upon occurrences. The first SAE case was reported to the Indonesia FDA (*BPOM*) on February 16; the second and third SAE cases will be reported to BPOM on March 9. The DSMB members are planning their discussion via teleconference on March 11.

The 2nd Site Monitoring Visit (SMV) is scheduled for April 15-17.

Save The Date

World TB Day, falling on **March 24** each year, is designed to build public awareness that tuberculosis today remains an epidemic in much of the world, causing the deaths of nearly one-and-a-half million people each year, mostly in developing countries.



The main sub-theme and message for this year is "**Reach, Treat, Cure Everyone**". World TB Day theme encourages local and state TB programs to reach out to their communities to raise awareness about TB. We don't have to fight TB alone; we should partner with others who are also caring for those most at risk for TB such as people with HIV infection or diabetes, and the homeless. Everyone has a role in ensuring that one day TB will be eliminated.

In light of this, the National Institute of Health Research and Development is holding a TB day event on March 11 – 12 in Ars Longa Auditorium, Building 3 floor 3, NIHRD.



Network Steering Committee Meeting and Network Annual Meeting

The next NSC Meeting will be held on **29-30 April 2015** in Jakarta at Hotel JS Luwansa, Jl. HR. Rasuna Said Kav. C-22, Jakarta Pusat, Daerah Khusus Ibukota Jakarta 12940, Indonesia.

FOR MORE INFORMATION

Please contact Mr. Dedy Hidayat or Ms. Yuyu Nuzulurrahmah at +62 21 42879189 ext. 102 or 112 during office hours (08.00 – 16.00)



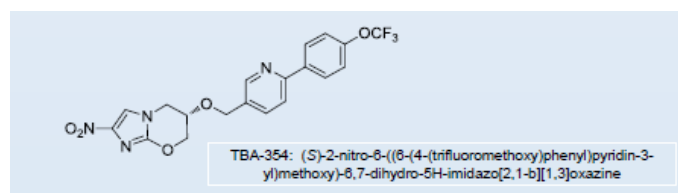
[A GLIMMER OF HOPE FOR TUBERCULOSIS TREATMENT]

Delamanid. A nitroimidazo-oxazole was granted conditional approval by EMA in April 2014. Information about this new drug, however, remains limited since it has only been through Phase IIb trial and studies for safety and efficacy. Sputum culture conversion rates in MDR-TB patients improve when Delamanid is added to existing regimen. However, the optimum duration, dose, and schedule for administering Delamanid still remain a question. Furthermore, Delamanid's ability to protect against emergence of resistance to other co-administered anti-TB drugs regimens demand to be studied. It is unclear which agents would be the most effective and least toxic when paired with Delamanid to treat drug-resistant TB.

PA-824. Another synthesized nitroimidazole that potentially contributes to novel regimens for TB is PA-824 (Pretomanid). The novel mechanism of action of PA-824 involves inhibition of the synthesis of mycobacterial proteins and lipids, but not nucleic acids. A triad of PA-824, Moxifloxacin, and Pyrazinamide (PaMZ) is potentially suitable for treating drug-sensitive and drug-resistant TB in 4 months, drastically improving treatment. This can be considered as a first step towards developing a single treatment regimen for both TB. PaMZ was the first novel multi-drug TB treatment to undergo clinical testing in the new regimen development paradigm. This multiple agents are expected to contribute in reducing the time needed to develop new antituberculosis regimens. This regimen is projected to be able to be effectively administered alongside common ARV treatments, therefore improving treatment options for patients co-infected by TB and HIV. Additionally, PaMZ regimen can be administered in a fixed dose for all patients, and will therefore be simpler for health systems to deliver and for patients to use.

TBA-354. The Global Alliance for TB Drug Development has pursued the synthesis and evaluation of over one thousand nitroimidazole analogs. To maximize the potential of nitroimidazole class, TBA-354 was selected as a potential next-

generation antituberculosis nitroimidazole following an extensive medicinal chemistry effort. TBA-354 has narrow spectrum and bactericidal in vitro against replicating and nonreplicating Mycobacterium tuberculosis, with potency similar to that of Delamanid and greater than that of PA-824. Having demonstrated advantages over the first-generation compounds, TBA-354 entered clinical testing in 2015.



The phase 1 randomized trial aims to evaluate the safety and tolerability of single oral doses of TBA-354 when it is administered to healthy adult subjects. The first human trial of TBA-354 is expected to be completed by the end of 2015, by enrolling 48 healthy adult volunteers at one study center in the United States. The Phase 1 program includes two clinical studies, a single ascending dose study and a multiple ascending dose study. Six cohorts of 8 subjects each (6 active and 2 placebo), with one cohort crossing over to assess food effect, are planned for evaluation. Safety will be assessed throughout the study; serial ECGs and serial blood samples will be collected for the safety and PK assessment of TBA-354. Dose escalation to the next cohort will not take place until the Sponsor, in conjunction with the Principal Investigator, has determined that adequate safety, tolerability, and PK from the previous cohort have been demonstrated to permit proceeding to the next cohort.

All of these new contrivances bring a glimmer of hope for tuberculosis treatment all over the world. In the coming decade, there are likely some newly developed drugs resulted from many high quality trials. As one of the leading clinical research networks on infectious disease in Indonesia, INA-RESPOND is prepared to conduct high quality clinical research. Let's just say, we are ready to take up the challenge and toss our hat into the ring.

Establishment of a Biorepository: Brief Overview of Some Essential Issues

by Agus Dwi Harso, Dona Arlinda, M. Karyana

The terminology of “biorepository” maybe not be known so well in Indonesia. However, the concept of storing biological specimens for future researches has been grasped by institutions such as the National Institute of Health Research and Development (NIHRD) in conjunction to its large-scale studies. According to guideline of the International Society for Biological and Environmental Repositories (ISBER) in 2012, biorepository is an actual or virtual entity that may receive, process, store or distribute biological specimens, and their associated data as appropriate, in support of a study or multiple studies. As the idea of biorepository is already familiar to its research practices, it is only natural that the NIHRD should proceed to set up an actual facility for biorepository to anticipate genetic and biomolecular era of research in Indonesia.

Originally, biorepository service is not intended for short term run. The US Department of Defense Serum Repository in Silver Spring, Maryland has samples stored from the HIV screening program back in 1985. John Hopkins Biological Repository (JHBR), which was established in 1984, currently consists of 1,500 square feet of biosafety level 2 laboratories on the Johns Hopkins Bloomberg School of Public Health (JHSPH) with additional 6,000 square feet in facility located 3 miles away from JHSPH, capable of holding 60 liquid nitrogen vapor phase cryogenic units. Nevertheless, a prototype model of biorepository service can still be started with as many as one freezer available in the existing laboratory for short-term storage. Such case may apply to a simple population-based collection model, i.e. biorepository that stores specimens obtained for defined study purposes. Further development should foresee future needs, allowing it to expand its capacity in line with the growing number of specimens it holds.

Because ensuring specimen quality for future research and managing the specimens are its priority, regular preventive maintenance program, backups,

and contingency plans are necessary. Biorepository is a controlled environment. Secure funding, quality assurance, quality control, SOPs, internal and external audits as well as documentation and reporting need to be put in place. As part of cold-chain of custody, the specimen collector (or investigator), handler and transporter must comply with Good Clinical and Laboratory Practice (GCLP) principles, in order for biorepository to have good quality specimens to begin with. Biorepository will provide active specimen-tracking system for storage and distribution purposes. Various softwares for specimen management system are available, such as Freezerworks™, Laboratory Data Management System (LDMS), Laboratory Information Management System (LIMS), etc.

Informed consent is another critical topic in biorepository service. The Declaration of Helsinki and ISBER Guideline (2012) require that the collection, storage, and use of human specimens and associated data should be conducted in a way that respects the individual and maintains privacy and confidentiality. Biorepositories should also adhere to and be kept up-to-date on relevant national human subjects regulations, privacy regulations, and other relevant national, state, and local laws. Subjects should have an informed choice about whether to



provide specimens and data to the repository and agree, where applicable, to future research use. The consent may be obtained for a specific research project, i.e. details of the project specifically outlined, or for unspecified future research providing general information about the possible future research uses.

With all that crucial points in mind, setting up a biorepository may not seem to be an easy task. However, the NIHRD will stay committed, and the development of a biorepository facility is already listed in its plan. The NIHRD realizes the value of biorepository as a crucial bridge for many areas of

research, especially researches to discover new drugs, new vaccines, or new diagnostic tools. Stored specimens can be retrieved, with respect to subject's consent, privacy and confidentiality, for testing the new intervention prior to the actual test on human. Moreover, retrieval of stored specimens will save much time and resources as the investigator will not repeat specimen collection phase, particularly if the subject of interest belongs to vulnerable group or subpopulation. The benefit of having a biorepository facility will outshine the vast investment made.

Quiz

by dr. Retna Mustika Indah.

To commemorate the world TB Day on March 24, we have trivia questions about TB drugs for you. The questions are really easy, and you can definitely answer them if you read our newsletters. So here you go... ☺

1. Together with INH, this drug is used as standard regimen in treatment of drug sensitive TB patients on continuation phase. This drug intensely red solid, and the small fraction which reaches body fluids is known for imparting a harmless red-orange color to the urine. What is the name of the drug?
2. Approved by FDA in December 2012, this drug becomes the first new drug with novel mechanism in over 40 years.

This diaryquinolines, hopefully, can bring a new hope in treating MDR TB. What is the name of the drug?

3. This new drug from nitroimidazole group inhibits the synthesis of mycobacterial proteins and lipids but not nucleic acids. The cocktail of this drug with moxifloxacin and pyrazinamide has potency to cure drug sensitive TB and MDR TB. What is the name of the drug?

Please email your answer to INA.Secretariat@s-3.com by March 27 for a chance to win a souvenir! Good luck!

INA-RESPOND Newsletter

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