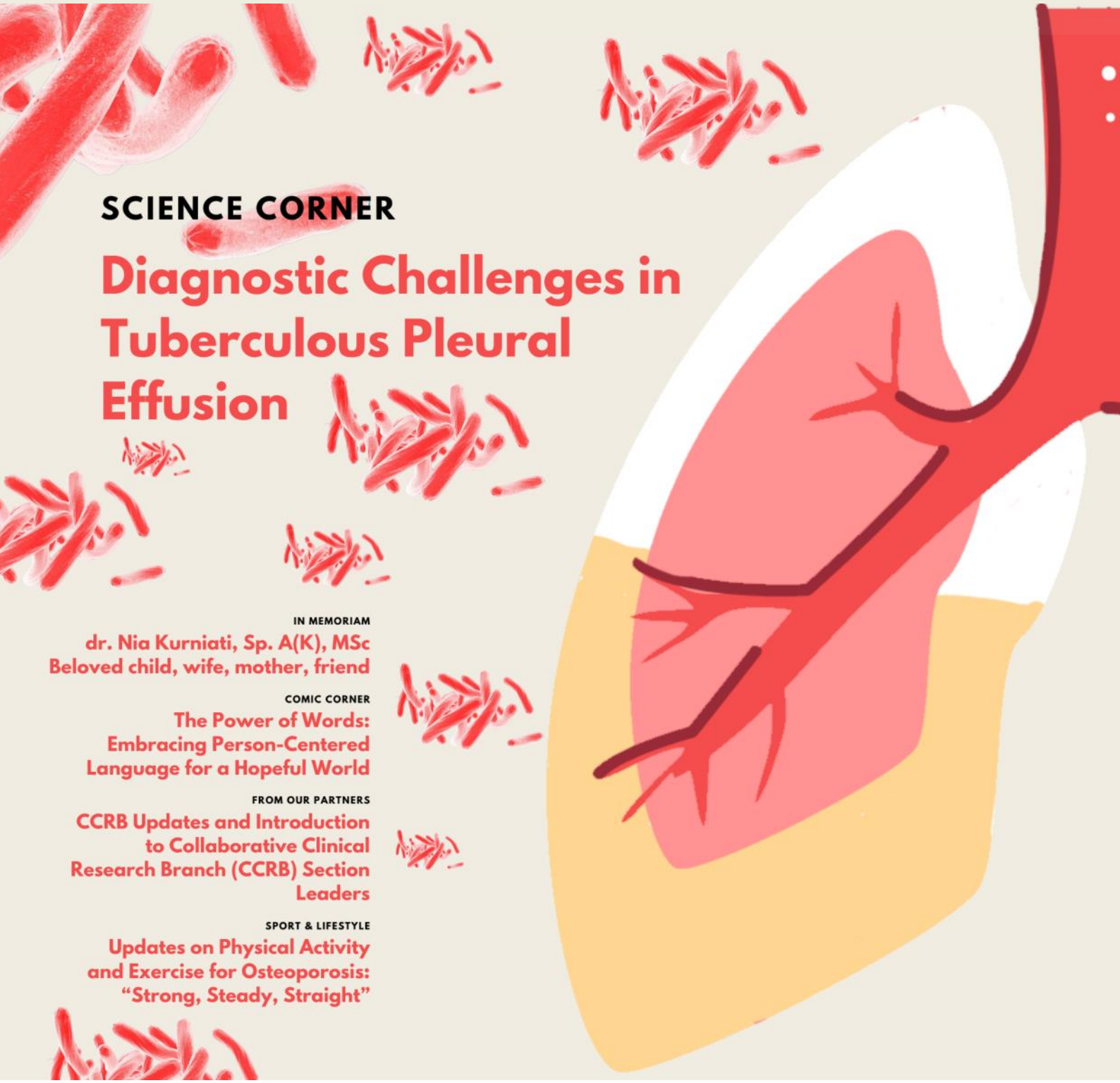
INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

February 2024



SCIENCE CORNER

Diagnostic Challenges in Tuberculous Pleural Effusion

IN MEMORIAM

dr. Nia Kurniati, Sp. A(K), MSc
Beloved child, wife, mother, friend

COMIC CORNER

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HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2024

MASTHEAD

INA-RESPOND newsletter

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SENIOR WRITERS

Adhella Menur, Aly Diana, Yan Mardian

REVIEWERS & CONTRIBUTING WRITERS

Adhella Menur, Risky Dwi Rahayu, Eka Windari R., Erni, I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Mila Erastuti, Nurhayati, Nur Latifah Hanum, Retna Mustika Indah, Restu Amalia, Riza Danu Dewantara,

.

THANK YOU

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INA-RESPOND Secretariat

Badan Kebijakan Pembangunan Kesehatan, Gedung 6, Lantai 3.
Jl. Percetakan Negara no.29,
Jakarta 10560
www.ina-respond.net

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INA-RESPOND Newsletter

InVITE & PROACTIVE Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Restu Amalia, Riza Danu Dewantara

InVITE

As of February 12, 2024, all 700 participants (100%) who enrolled in the study have completed their participation. The study was conducted at three different sites: Site 01 completed Visit 5 on January 24, 2024; Site 02 (TC Hillers Hospital) completed Visit 5 on November 16, 2023; and Site 03 (Dr. Ansari Saleh Hospital) completed Visit 5 on January 4, 2024. The details of the visits for each site are listed in Table 1.

Out of the 700 participants who ended their participation, 639 (91.29%) completed the study, while 44 (6.29%) withdrew. Reasons for withdrawal included decisions by participants, personal reasons, or loss of interest. Additionally, three (0.43%) participants were excluded from the study because they did not receive the complete vaccine regimen within 12 months of enrollment. Two (0.29%) participants were not allowed to continue as it was not in their best interest, and one (0.14%) participant was non-compliant with study procedures. Regrettably, one (0.14%) participant passed away during the study, and ten (1.43%) participants had other reasons for ending their participation.

The study has also been monitoring symptomatic visits among participants. Table 2 provides details of these visits as of February 12, 2024. It is important to emphasize that while some participants have experienced symptoms of COVID-19, this does not necessarily indicate that they have contracted the virus.

As of January 25, 2024, the Material Transfer Agreement has been approved by *Kepala Badan Kebijakan Pembangungan Kesehatan (BKPK)* / Health Policy Agency. INA-RESPOND and NIAID are currently discussing preparations for shipping specimens from the Reference Laboratory to the Central Laboratory.

Site	Symptomatic Visit		
	# of visit	Positive	Negative
01	105	62	43
02	14	6	8
03	2	1	1
Total	121	69	52

Table 2. Symptomatic Visit Details per Feb 12, 2024

Site	Screening / Visit 1	Enrollment Failure	Enrolled	Ongoing	Add. Visit 1	Visit 2	Add. Visit 2	Add. Visit 3	Visit 3	Agree Ext.	Not Agree Ext.	Ext. Visit 4	Ext. Visit 5
01	345	2	343	0	88	326	314	306	315	285	30	277	272
02	228	1	227	0	97	214	191	188	195	151	44	151	148
03	130	0	130	0		130			129	95	34	95	92
Total	703	3	700	0	185	670	505	494	639	531	108	523	512

Table 1. Details of Visits per site per Feb 12, 2024

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In addition to the preparation of PROACTIVE primary and additional manuscripts previously mentioned, we are also conducting a scoping review on HIV research in Indonesia since the first HIV case was reported in the country in 1987. The goal is to comprehensively understand HIV research in Indonesia and identify gaps where further research is needed. This activity involves INA-RESPOND Secretariat staff and Warm-based Research Assistants from all sites. We found around 1,500 international publications covering all aspects of HIV, from epidemiology and laboratory to clinical and socio-behavioral studies. Our first scoping review project focuses on research concerning children living with HIV in Indonesia. The articles involving pediatric patients were screened, categorized, and later selected for discussion. This review will support the preparation of a PROACTIVE manuscript on pediatric subjects.

INA-RESPOND Secretariat Staff, along with Research Assistants (RAs), have established an "HIV Journal Club." This club meets online every two weeks to discuss selected HIV articles conducted in Indonesia to keep abreast of current knowledge, learn to critique and appraise research, and enrich references for manuscript writing. Site investigators, Secretariat staff, and RAs attend the meetings. RAs, in turn, present the articles and lead the ensuing discussion.

The background of this study highlights the critical need to maintain effective antiretroviral therapy (ART) and its association with an adequate virological response. Managing children and adolescents living with HIV presents substantial challenges, notably in sustaining effective ART. Significant threats to this endeavor include poor treatment adherence and drug resistance. HIV viral load testing is the preferred method for monitoring the response to ART and serves as an essential tool for identifying issues with treatment adher-

Presenters	Article Title	Journal Information	Meeting Schedule
dr. Myrna EA (Surabaya) dr. Rizki AB (Makassar)	Early and late virologic failure following virologic suppression in HIV-infected Asian children and adolescents.	Mu W, et al. J Acquir Immune Defic Syndr. 2019.	12 January 2024
dr. Cintya ND (Tangerang) dr. NLP Ariastuti (Bali)	Association between human immunodeficiency virus infection and arterial stiffness in children.	Charakida, et al. Antivir Ther. 2009.	16 January 2024
dr. Vitia ANL (Yogyakarta) dr. Ivana YH (Tangerang)	"I can live a normal life": Exploring adherence to antiretroviral therapy in Indonesian adolescents living with HIV.	Nuraidah, et al. Belitung Nurs J. 2022.	19 January 2024
dr. Erni (Semarang) dr. Putri PP (Jakarta)	Incidence of post suppression virologic rebound in perinatally HIV-infected Asian adolescents on stable combination antiretroviral therapy.	Sudjaritruk T, et al. J Adolesc Health. 2017.	23 January 2024
dr. Dhiny RA (Makassar) dr. Titin DM (Jakarta)	HIV-infected children in the Asia-Pacific region with baseline severe anemia: antiretroviral therapy and outcomes.	Lumbiganon P, et al. Asian Biomed (Res Rev News). 2016.	26 January 2024
dr. Fransisca M (Tangerang) dr. Rifa'ah R (Surabaya)	Immunological outcomes after six months with first line antiretroviral therapy: a lesson from Yogyakarta, Indonesia.	Pangarungan M & Arguni E. J Infect Dev Ctries. 2018.	02 February 2024

HIV Journal Club – 1st

CLINICAL SCIENCE

Early and Late Virologic Failure After Virologic Suppression in HIV-Infected Asian Children and Adolescents

Weiwei Mu, MD, MPH, Adam W. Bartlett, FRACP,† Torsak Bunupuradah, MD,‡ Kulkanya Chokephaibulkit, MD,§ Nagalingeswaran Kumarasamy, MBBS,‖ Penh Sun Ly, MD,¶ Rawiwan Hansudewechakul, MD,# Lam Van Nguyen, MD,** Pagakrong Lumbiganon, MD,†† Tavitiya Sudjaritruk, MD, ScM, PhD,‡‡ Thahira A. Jamal Mohamed, MBBS,§§ Nik Khairulddin Nik Yusoff, MBBS, DTM&H,‖‖ Khanh Huu Truong, MD,¶¶ Viet Chau Do, MD,## Moy Siew Fong, MBBS,*** Revathy Nallusamy, MBBS,††† Nia Kurniati, MD, PhD,‡‡‡ Dewi Kumara Wati, MD,§§§ Annette H. Sohn, MD,‖‖‖ Azar Kariminia, PhD,† and Fujie Zhang, MD, PhD,*¶¶¶ for the TREAT Asia Pediatric HIV Observational Database of IeDEA Asia-Pacific*

J Acquir Immune Defic Syndr • Volume 80, Number 3, March 1, 2019

ence and drug resistance. Currently, virologic failure has been reported in 25–34% of children and adolescents receiving ART. A better understanding of virologic failure in pediatric populations is crucial as it will guide the development and implementation of interventions, thereby optimizing the durability of ART regimens, improving HIV outcomes, and aiding in achieving the UNAIDS target of viral suppression.

The study aimed to describe the incidence of virologic failure and identify its associated factors within the TREAT Asia pediatric HIV Observational Database (TApHOD) cohort, a regional study in South and Southeast Asia. Virologic failure is defined as at least one HIV viral load of ≥1,000 copies/mL following virologic suppression, achieved after receiving six months of continuous combination ART (cART) in conjunction with a documented HIV viral load of <400 copies/mL 5–12 months after beginning continuous cART. Conducted in an Asian cohort across 16 pediatric HIV services in six countries (Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam) from 2005 to 2014, the study analyzed patients under 20 years who achieved virologic suppression and underwent subsequent viral load testing. It presented participants' characteristics at the initiation of cART and upon virologic suppression, the cumulative incidence of virologic failure, and the factors at virologic suppression associated with early and late virologic failure. Early virologic failure is defined as occurring ≤12 months from the initial virologic suppression, while late virologic failure occurs >12 months after.

Among the 1,105 individuals analyzed, 182 (17.9%) experienced virologic failure. The median age at virologic suppression was 6.9 years, and the median time to virologic failure was 24.6 months post-suppression. The incidence rate for a first virologic failure event was 3.3 per 100 person-years. Factors associated with late virologic failure at the time of virologic suppression included older age, treatment in predominantly rural clinic settings, a history of tuberculosis (TB), the use of protease inhibitor (PI)-based regimens, and previous early virologic failure. No risk factors were pinpointed for early virologic failure. Approximately one in five children and adolescents in the cohort experienced virologic failure at a median time of 2 years after achieving virologic suppression. Factors such as older age at the initiation of cART, a history of TB co-infection, the use of PI-based regimens, treatment in rural clinic settings, and a history of early virologic failure were linked with long-term virologic failure. To meet the UNAIDS target, there is a necessity to improve the capacity for early HIV diagnosis and the initiation of cART in HIV-exposed infants and children, conduct regular HIV viral load testing, and implement targeted interventions to manage complex treatment scenarios, including those involving adolescents, TB co-infection, and cases of poor virologic control.

Dr. Nia Kurniati's passing on January 17, 2024, marks a profound loss for the medical community, especially our INA-RESPOND network family. Her dedication to improving pediatric HIV care, her contributions to research, and her role as a mentor and educator leave a lasting legacy that will continue to influence the field and the lives of those she touched.

Dr. Nia Kurniati, Sp.A(K), MSc, was a respected pediatric HIV specialist and researcher who made significant contributions to the field of pediatric HIV care and research, both within Indonesia and internationally. Born on August 8, 1965, in Bandung, Indonesia, she pursued her medical degree at the Faculty of Medicine, Universitas Indonesia, and further specialized in Pediatric Allergy and Immunology. Dr. Kurniati obtained her Master of Science in Clinical Epidemiology from Utrecht University in 2016. She continued to advance her academic and professional career by participating in a doctoral program at the Faculty of Medicine, Universitas Indonesia (FKUI), where she defended her dissertation titled "*Gagal Virologis terhadap Antiretroviral Lini Satu pada Anak Dengan Infeksi HIV: Faktor Yang Memengaruhi serta Resistensi yang Didapat*" on July 21, 2022. This work focused on virological failure in children with HIV infection treated with first-line antiretroviral therapy, factors influencing this outcome, and the resulting resistance.

As a researcher, Dr. Nia was internationally renowned. She served as an Indonesian pediatrician in TREAT ASIA (Therapeutics Research, Education, and AIDS Training in Asia), a network comprising clinics, hospitals, and research institutions collaborating with civil society to ensure the safe and effective delivery of HIV/AIDS treatment across Asia and the Pacific. Her collaboration within this network, involving the analysis of a pediatric HIV observational database, has yielded more than 30 publications addressing HIV infections in children and adolescents. These publications cover a wide array of topics, ranging from drug resistance, epidemiology, social behavior, and education, to comorbidities and co-infections, as well as virological, clinical, and immunological outcomes.

Collaborating with Julius Global Health at the Department of Pediatrics, University of Melbourne, Australia, and CEEBM at the Medical Faculty, Universitas Indonesia, Dr. Nia authored six publications focused on cardiovascular disease in children with HIV. Additionally, her publications on COVID-19, *Streptococcus pneumoniae*, *Haemophilus influenza*, and leukemia reflected her interest in non-HIV research as well. In fact, she is the senior author of two publications related to the last two topics. These publications, titled "Nasopharyngeal Carriage and Antimicrobial Susceptibility Profile of *Haemophilus influenza* among Patients with HIV" and

"The Effect of the Combination of Steroid and L-asparaginase on Hyperglycemia in Children with Acute Lymphoblastic Leukemia," showcase her significant contributions. In total, 48 of her publications are listed in PubMed, demonstrating her dedication and productivity as a researcher.

Furthermore, her manuscripts have also been published in Pediatrica Indonesiana, the official journal of the Indonesian Pediatric Association. Regarding HIV, she reported the incidence of HIV-infected infants born to HIV-infected mothers under prophylactic therapy as outcomes of the PMTCT program at Cipto Mangunkusumo Hospital and analyzed virological failure of first-line antiretroviral therapy in children along with its associated factors.

Prior to her illness, Dr. Nia played an active role in the discussions surrounding the first PROACTIVE manuscript and the conceptual planning for the PROACTIVE Pediatrics manuscript. While her departure is premature, it should not hinder our commitment to advancing this work. On the contrary, it should serve as motivation to persevere and fulfill her vision that the outcomes of this study will bring substantial benefits to HIV clinicians, researchers, communities, governments, and non-governmental organizations to enhance the provision of optimal care for HIV-infected children, who, until now, remain reliant on antiretroviral therapy throughout their lives.

In Islamic belief, three things follow they who have passed away: the charity they gave, the knowledge they taught, and a righteous child who prays for them. We are sure that Dr. Nia has accomplished these three things. She was a wonderful person who dedicated her knowledge to children's health, education, and research in Indonesia. Her legacy will inspire young medical doctors not only to focus on clinical practice but also to engage in impactful research. Her shared knowledge and good deeds will illuminate her journey hereafter, inshaAllah.

INA-RESPOND Newsletter

CCRB UPDATES AND INTRODUCTION TO CCRB SECTION LEADERS

By: Mary Smolskis, BSN, MA, Operations and Strategy Management Section Chief
Stephen Migueles, M.D., CCRB Science Section Chief

As of June 2023, the Office of Planning and Operations Support (OPOS) merged with the Collaborative Clinical Research Branch (CCRB) within the Division of Clinical Research (DCR). In this unification, the CCRB has introduced two new sections: the Science Section and the Operations and Strategy Management Section. The Science Section is dedicated to providing scientific guidance and oversight and establishing working relationships with host country government ministries and partners. Meanwhile, the Operations and Strategy Management Section will act as a resource for operations, logistics, and training for clinical trials/studies from the early stage of protocol development through the lifecycle of protocols. This includes the identification and coordination of all resources required across special projects, developing innovative approaches to operational challenges while remaining within budget requirements, maintaining the availability and offering of relevant training programs across special projects, and keeping strategic management in alignment with the DCR and special projects' strategy planning, all while coordinating closely with the CCRB Science Section.

Mary Smolskis has been with the National Institute of Allergy and Infectious Diseases (NIAID) since 1987. She became the new Director of the Office of Planning and Operations Support as of January 2023. Prior to this role, she served as a Clinical Research Oversight Manager in the DCR for 15 years. Ms. Smolskis officially transitioned as the new Section Chief in June 2023. Her years of profound expertise in clinical research support initiatives in the Division of Clinical Research at NIAID. Her leadership guides the team's ceaseless endeavors in pioneering result-driven research in ever-changing times. Notably, her role in PREVAIL, LaRed, and DCR ICC operations co-lead are examples of the multifaceted areas of focus in CCRB and DCR's research and development.

Dr. Stephen Migueles
Chief of Science Section, CCRB

Dr. Migueles will head the Science Section in the CCRB. He joined the National Institute of Allergy and Infectious Diseases in 1997 as a Clinical Associ-

ate in the Laboratory of Immunoregulation and was commissioned as a Medical Officer in the U.S. Public Health Service (USPHS). He became a Staff Clinician in 2005, was promoted to CAPT (O-6) in the USPHS in 2010, and became a Senior Research Physician in 2017. He maintains active certification in Internal Medicine and Infectious Diseases. Currently, Dr. Migueles is the head of the Cellular Immune Response Unit, with a research focus on the cellular response to HIV, SARS-CoV-2, mechanisms of durable immunologic control of HIV in patients, immunology of vaccine-induced responses, and a cohort of people living with HIV infection in West Africa (Liberia). He will officially transition to his new role in the CCRB in February 2024. The Collaborative Clinical Research Branch is thrilled to have Dr. Migueles and Ms. Smolskis in their new leadership appointments and looks forward to their role in promoting the mission and vision of the branch.

DCR Special Projects Smartsheets is an exciting source with access to information across special projects. INA-RESPOND has a dashboard available full of analytics in protocol timelines, enrollment summaries, publications, and much more. For more details, user access, and questions, please contact Katie Watkins at katie.watkins@nih.gov or Kristine Nagales at kristine.nagales@nih.gov.

NIAID DCR CCRB recently refreshed its web pages with up-to-date information. Rich with resources and information, worldwide partnerships and the latest studies can be found at https://www.niaid.nih.gov/about/collaborative-clinical-research-branch and INA-RESPOND's network at https://www.niaid.nih.gov/research/ina-respond-network. Please contact Kristine Nagales for details and questions at kristine.nagales@nih.gov.

World Cancer Day 2024's theme is "Close the Care Gap," targeting inequalities in cancer care globally. Marked annually on February 4, the campaign by the Union for International Cancer Control (UICC) aims to bridge disparities in access to cancer services, highlighting how factors like income, education, and geography impact care availability. Cancer, as one of the leading causes of death worldwide, presents diverse challenges that require tailored treatments. The initiative stresses the importance of equitable healthcare access to improve outcomes for all individuals, irrespective of their background. Cancer care is significantly underserved in developing countries due to limited resources, infrastructure, and healthcare access. This disparity results in late-stage diagnoses and lower survival rates, emphasizing the importance of global support and local initiatives to improve cancer care and awareness.

With this spirit in mind, why not become involved in the worldwide movement to end the cancer care gap? Let's educate ourselves, speak out, and make a difference. To make sure that everyone has equal access to cancer care, we can get involved with local and global health organizations, give, volunteer, and raise awareness. The battle against cancer can be won if we are united. –dh

Source: Campaign theme I World Cancer Day

INA-RESPOND Newsletter

DIAGNOSTIC CHALLENGES IN TUBERCULOUS PLEURAL EFFUSION

By: Ismi Wahyu Riyanti, Adhella Menur

SCIENCE CORNER

Pleural effusion overview

The pleural cavity is a space between the parietal and visceral pleurae that aids in the optimal functioning of the lungs during breathing. Normally, a small physiological amount of pleural fluid (0.1-0.3 mL per kg) resides within this space. This delicate balance of fluid is maintained by oncotic and hydrostatic pressures and by lymphatic drainage. If there is any disturbance leading to an excessive and abnormal accumulation of fluid in the pleural cavity, it is called pleural effusion (PE). To date, PE has remained a significant cause contributing to hospitalization, increasing medical costs, morbidity, and mortality. The actual burden of PE is uncertain since only a few epidemiological studies have been published, which are mostly retrospective, single-center, and based in Europe and the United States. In the US, it is estimated that there are 1.5 million new cases of PE annually.

PE can occur from various disorders of the pleura itself, lung parenchyma, and other organs or from systemic disorders. According to the underlying pathophysiology, PE is classified into transudates (e.g., heart failure, liver cirrhosis, nephrotic syndrome, or hypoalbuminemia) and exudates (e.g., inflammation, infection, or malignancy). The ability to distinguish between the two types of PE is crucial for patient management. For more than 50 years, the Light's criteria have been used by clinicians as the benchmark test combination for differentiating between transudates and exudates. The Light's criteria classify PE based on the absolute lactate dehydrogenase (LDH) value, the pleural fluid to serum LDH ratio, the concentration of pleural fluid protein, and the pleural fluid to serum protein ratio.

Tuberculosis (TB) is one of the top four etiologies that account for about 75% of PE cases, along with heart failure (HF), malignancy, and pneumonia. In 2019, the WHO reported that 15% of global TB cases were associated with extrapulmonary TB (EPTB), and tuberculous pleural effusion (TPE) became the most dominant form in adults. The incidence of TPE varies from 3% to 30%, particularly high in TB-endemic areas and among individuals with comorbidities such as HIV. Indonesia is the second-highest TB burden country globally; therefore, TPE should be a significant concern. Even though primary TPE may resolve spontaneously, patients frequently develop active TB later. Additionally, if left untreated in immunocompromised patients, TPE can become complicated and fatal. TPE is unique due to its paucibacillary nature (low bacterial count), causing a diagnostic dilemma in resource-constrained settings. In this edition, we will discuss TPE and the challenges in diagnosis.

Tuberculous pleural effusion

Tuberculous pleural effusion (TPE) may occur in primary tuberculosis (TB) or with reactivation of the disease. It may present as isolated extrapulmonary TB or coexist with pulmonary TB. TPE is classified as an exudative type of pleural effusion (PE),

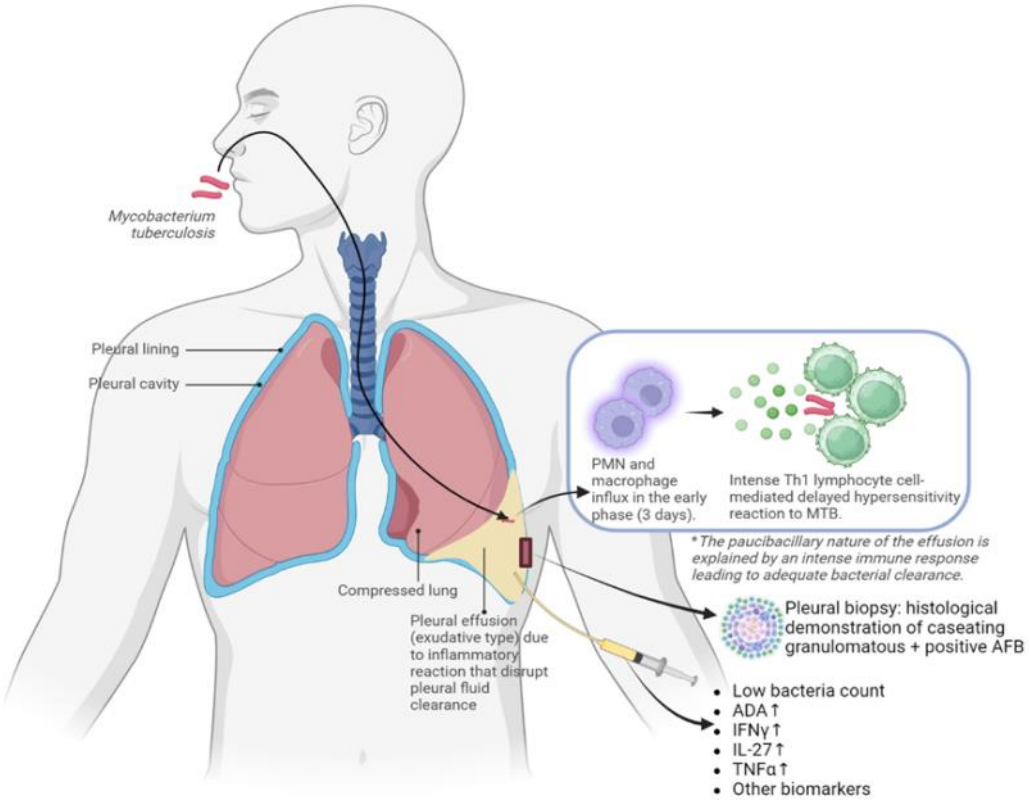

Figure 1. Tuberculous pleural effusion (TPE). Inspired by a review from Vorster MJ, et al., 2015, doi: 10.3978/j.issn.2072-1439.2015.02.18. Created with Biorender.com

and its incidence is linked to the local disease burden, population characteristics, and socioeconomic status. For example, the TB burdens in Malaysia and Nigeria in 2016 were estimated at approximately 92 and 219 cases per 100,000 population, respectively. Consequently, TB was identified as the major etiology of PE, followed by malignancy. In contrast, a study in Spain in 2016 reported that TPE was only the fourth leading cause (9%) of PE after malignancy (27%), heart failure (21%), and pneumonia (19%). Furthermore, in the US, heart failure, pneumonia, and malignancy were predominantly attributed as the causes of PE rather than TB.

Although the pathogenesis has been debated, the current consensus agrees that TPE represents a delayed hypersensitivity reaction precipitated by Mycobacterium tuberculosis (MTB) antigens in the pleural cavity. It is marked by the accumulation of inflammatory cells and the significant presence of chronic effusion. In the absence of overt parenchymal lung disease, MTB is believed to access the pleural cavity following the rupture of a subpleural caseous focus. The infection in the pleural space triggers an early response by a rapid influx of macrophages and neutrophils. Lymphocyte T-helper type 1 (Th1) cells are involved in subsequent stages, with the release of adenosine deaminase (ADA) and the formation of pleural granulomas. The cytokine milieu favors a Th1 cell response with high levels of gamma interferon (IFN-γ), interleukin-12 (IL-12), and other related cytokines. This robust Th1 cell response, along with the compartmentalization of the pleural fluid and effective containment of MTB, is thought to be responsible for the paucibacillary nature of these effusions. A minority of patients progress from the lymphocytic phase to a second, neutrophil-predominant phase, presenting loculated effusion or frank empyema, which results in a higher rate of MTB culture positivity.

Diagnostic challenges in tuberculous pleural effusion

The gold standard for TPE diagnosis is the detection of MTB in pleural fluid or pleural tissue or histological demonstration of caseating granulomata on pleural biopsy, ideally in the presence of acid-fast bacilli (AFB). However, the diagnosis of TPE is inevitably hindered due to the low detection rate (paucibacillary nature) and long culture turnaround times. Limited access and skill to perform pleural biopsies, whether by closed pleural biopsies, thoracoscopy, or open surgical biopsies, also complicates diagnosis challenges.

In a suspected TPE case, it is still essential to obtain a sputum culture (expectorated or induced), even in the absence of obvious parenchymal lung involvement, especially in high TB burden settings. In those settings, the diagnosis of TPE is frequently concluded in patients who present with predominantly lymphocytic exudates and a high level of adenosine deaminase (ADA) in the pleural fluid. However, clinicians still face difficulty in differentiating TPE from malignancy and parapneumonic pleural effusion (PPE) due to similar biochemistry and cellular features. TPE and malignancy often present as lymphocytic effusions, while some cases

Strategy	Challenges and comments
Sputum and broncho alveolar lavage (BAL) microbiological examination	Non-induced sputum culture has a low yield of 0–30%. Induced sputum and BAL culture may increase the yield up to 55%. Need to evaluate the role of sputum nucleic acid amplification (NAA) molecular studies such as Xpert MTB/RIF in the context of TPE diagnosis.
General/ basic pleural fluid analysis (from needle aspiration/ thoracocentesis)	TPE is straw-colored exudates with elevated LDH levels commonly exceeding 500 IU/L and protein level >30 g/L in 55-77% cases. Most TPE have >50% lymphocytes, with some having >90%. However, neutrophils may predominate in the first few days of the effusion. Chronic effusions due to other etiologies often have a high lymphocyte ratio of 50% or more.
Pleural fluid microbiological examination	Pleural fluid AFB smear has a low yield of 0-10%, except in TB empyema, loculated effusions, and HIV-positive patients due to impaired bacterial clearance (the yield increased to 20%). The yield of MTB culture of pleural fluid depends on the culture medium used (solid media 12-30% and liquid media up to 70%). Xpert MTB/RIF: sensitivity 50.9%, specificity 99.2% compared to standard culture. Sensitivity 18.4%, specificity 98.2% compared with a composite reference standard (presence of caseating granulomas ± positive culture). Xpert MTB/RIF Ultra: improved sensitivity compared with both culture (68%) and composite reference standard (47%); specificity is slightly lower than Xpert (97%).
Pleural fluid adenosine deaminase (ADA; a purine-degrading enzyme found in all cells, particularly monocytes and lymphocytes)	There is a wide range of cut-off values used by authors, but in most studies, the common threshold was 40-70 U/L. ADA >40 U/L has shown a sensitivity of 92-100% and a specificity of 60-90%. In countries with low TB burdens, the negative predictive value remains high. ADA should not be interpreted independently; clinicians must be aware of situations that may increase the likelihood of both the false-negative (e.g., early phase, smoker, and elderly patients) and false-positive (PPE, rheumatoid effusion, mesothelioma, lymphoid malignancy, and lung cancer).
Pleural fluid unstimulated IFN-γ	Elevated pleural fluid unstimulated IFN-γ has shown a pooled sensitivity of 93% and specificity of 96% in diagnosing TPE. The optimum cut-off has not yet been established, and the assay remains expensive. Several patients with varying neoplastic disorders had significantly elevated IFN levels.
Pleural fluid IL-27	When used to differentiate between TPE and malignant effusion: sensitivity 93% and specificity 97%. The combination of IL-27 plus IFN-γ and/or ADA contributed to increased diagnostic accuracy for discriminating TPE from non-TPE.
Thoracoscopy	It yields large samples of pleural tissue with a diagnostic accuracy of >90%. It needs special infrastructures and skilled operators, which can be time-consuming and may lead to complications.
Closed needle pleural biopsy	Lower diagnostic yield than thoracoscopy. Diagnostic in 60–80% of cases when performed by a skilled operator. Recommended to obtain at least six samples at the time of pleural biopsy.

Table 1. Summary of several strategies and challenges in the diagnosis of tuberculous pleural effusion

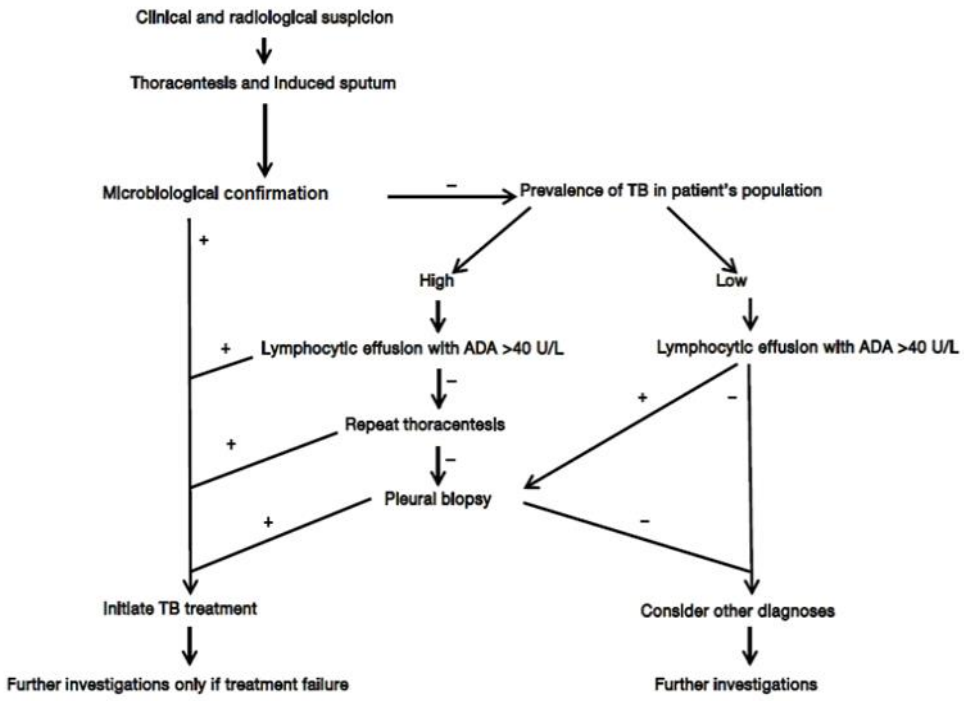

Figure 2. A suggested algorithm for the diagnostic evaluation of a patient who presents with a clinical and radiological suspicion of TPE. Microbiological confirmation includes positive AFB smear microscopy, Xpert MTB/RIF or positive culture on sputum or pleural fluid. A high TB prevalence is ≥125 per 100,000 population (Vorster MJ et al., 2015).

of TPE and PPE present as neutrophilic effusions. The diagnostic challenge between TPE and PPE is prominent in multi-endemic regions since both diseases are prevalent. Furthermore, some cases of PPE, particularly complicated PPE (CPPE), present with elevated ADA levels similar to those of TPE. Therefore, accurate, simple, and safe diagnostic tools are needed to address these challenges.

Numerous studies have investigated the potential use of other pleural fluid biomarkers, such as C-reactive protein (CRP), procalcitonin (PCT), presepsin, tumor necrosis factor-alpha (TNF-α), lysozyme, hyaluronic acid, neopterin, leptin, fibronectin, and cell-free DNA, with inconclusive results. There are also novel biomarkers such as pleural fluid nicotinamide phosphoribosyltransferase (NAMPT) and MTB HspX protein using a novel aptamer-linked immobilized sorbent assay (ALISA). NAMPT does not appear to have a benefit over ADA in distinguishing TPE from malignant PE, but it still has diagnostic ability, with a cutoff value of 31.93 ng/mL (sensitivity of 70% and specificity of 100%). The MTB HspX ALISA showed promise as a potential biomarker for TPE diagnosis with a sensitivity of 93% and specificity of 98% compared to the composite reference standard in one study.

Pleural fluid biomarker studies are still limited in Indonesia, primarily conducted as theses by residents in internal medicine, pulmonology, clinical pathology, or microbiology with small sample sizes. To our knowledge, there have been only three international publications from Indonesia: the use of IGRA with the ELISPOT method performed on pleural fluid mononuclear cells (PFMC) in 2016, a comparison of pleural fluid TNF-α in TPE and non-TPE in 2018, and an evidence-based case report on the diagnostic value of pleural fluid Cancer Antigen 125 (CA-125) in 2023. Therefore, there is a significant research gap that needs to be addressed.

A practical diagnostic approach is suggested in Figure 2 (different or updated versions may be available in each country). In conclusion, TPE should be appropriately diagnosed because the

patient is at risk of developing a serious form of pulmonary or extrapulmonary TB. Combining strategies (e.g., microbiological analysis + more than one pleural fluid biomarker) may improve the diagnosis of TPE. Given the high number of people infected with TB worldwide and the increasing number of TPE cases, the threat of drug-resistant TB is also worrying. Progress in finding more accurate biomarkers to aid diagnosis and more sensitive molecular-based testing is expected to improve diagnosis and provide crucial information on drug resistance profiles. It is such a waste to fail to diagnose this treatable infectious disease.

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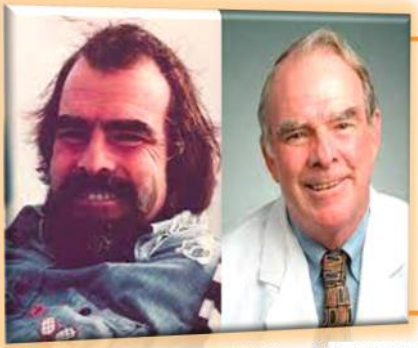

Lightening fact!

Dr. Richard W. Light (1942–2021) began his study on differentiating transudates and exudates pleural effusion when he was a pulmonary fellow at Johns Hopkins Hospital. Over a 2-year study period, he empirically defined the Light's criteria. He submitted the first abstract to the American Thoracic Society meeting in 1971, **but it was rejected!** In April 1972 he sent an original manuscript to Annals of Internal Medicine, which was accepted with minor changes. Imagine if he gave up on his research 😊 **So, never give up!**

Must read: Light, R.W. The story behind Light's criteria (2010), Pérez, J.M.P. & Newman, J.H. Giants in chest medicine: Richard W. Light, MD (2014), and Porcel, J.M. The eponymous Dr. Richard W. Light: father of pleural medicine (2021).

INA-RESPOND Newsletter

UPDATES ON PHYSICAL ACTIVITY AND EXERCISE FOR OSTEOPOROSIS: "STRONG, STEADY, STRAIGHT"

By: Risky Dwi Rahayu

Low bone mass and deterioration of bone tissue are common characteristics of osteoporosis. Globally, over 200 million women suffer from osteoporosis. In Indonesia, the prevalence of osteoporosis in women aged 50-80 years old is 23%, increasing to 53% in women aged more than 80 years old. Osteoporosis leads to fractures due to the fragility it causes, although individuals affected often have no symptoms or pain. One in three women over 50 years old will experience an osteoporotic fracture, although men can also be affected, albeit at a lower ratio. The fractures mostly occur in the spine, hip, or wrist. Mechanisms of injury are quite simple, such as falls from standing height, minor bumps, or bending-over activities.

Several groups are susceptible to osteoporosis: older individuals, those who have had a previous fracture after the age of 50, those with a family history of osteoporosis, those with early menopause, smokers, individuals with a low body mass index, those with malabsorption problems, those with long-term corticosteroid use, and those with excessive alcohol intake. Assessment of bone mineral density with Dual X-ray Absorptiometry (DXA) is used to confirm a diagnosis of osteoporosis with a T-score < -2.5. The risk of osteoporotic fracture in the next 10 years can be calculated effortlessly with the Fracture Risk Assessment Tool (FRAX), which is accessible through an online calculator.

Exercise and physical activity are active components of the prevention and management of osteoporosis, offering improvements in bone strength and a reduction in the risk of falls. The current UK consensus statement on physical activity and exercise for osteoporosis identifies three key objectives in its recommendation of exercise for individuals with confirmed osteoporosis or significant risk of fracture (with or without osteoporotic fracture), referred to as "Strong, Steady, and Straight".

Strong: Exercise and physical activity can promote bone strength and prevent fractures by performing progressive resistance training and weight-bearing/ impact activities. Ideally, the resistance training should be supervised to ensure proper technique and to lower the injury risk. The frequency should be 2-3 days per week. The intensity should be maintained at 8-12 repetitions in 2-3 sets. The initial load should be lower to ensure correct technique, and then the load can be increased gradually. All muscle groups should be targeted, which can be achieved through two modes:

A. One exercise each for legs, arms, chest, shoulders, and back using exercise bands, weights, or body weight.

B. Eight exercises targeting major muscle groups of the hip and spine, including weighted lunges, hip abduction/adduction, knee extension/ flexion, plantar-dorsiflexion, back extension, reverse chest fly, and abdominal exercises (avoiding loaded spinal flexion).

However, these supervised exercises may be performed by only a small portion of the population. Hence, the Consensus also recommends engaging in sports or leisure activities that promote muscle strength such as circuit training, rowing, Pilates, yoga, stair climbing, sit-to-stands, heavy housework or

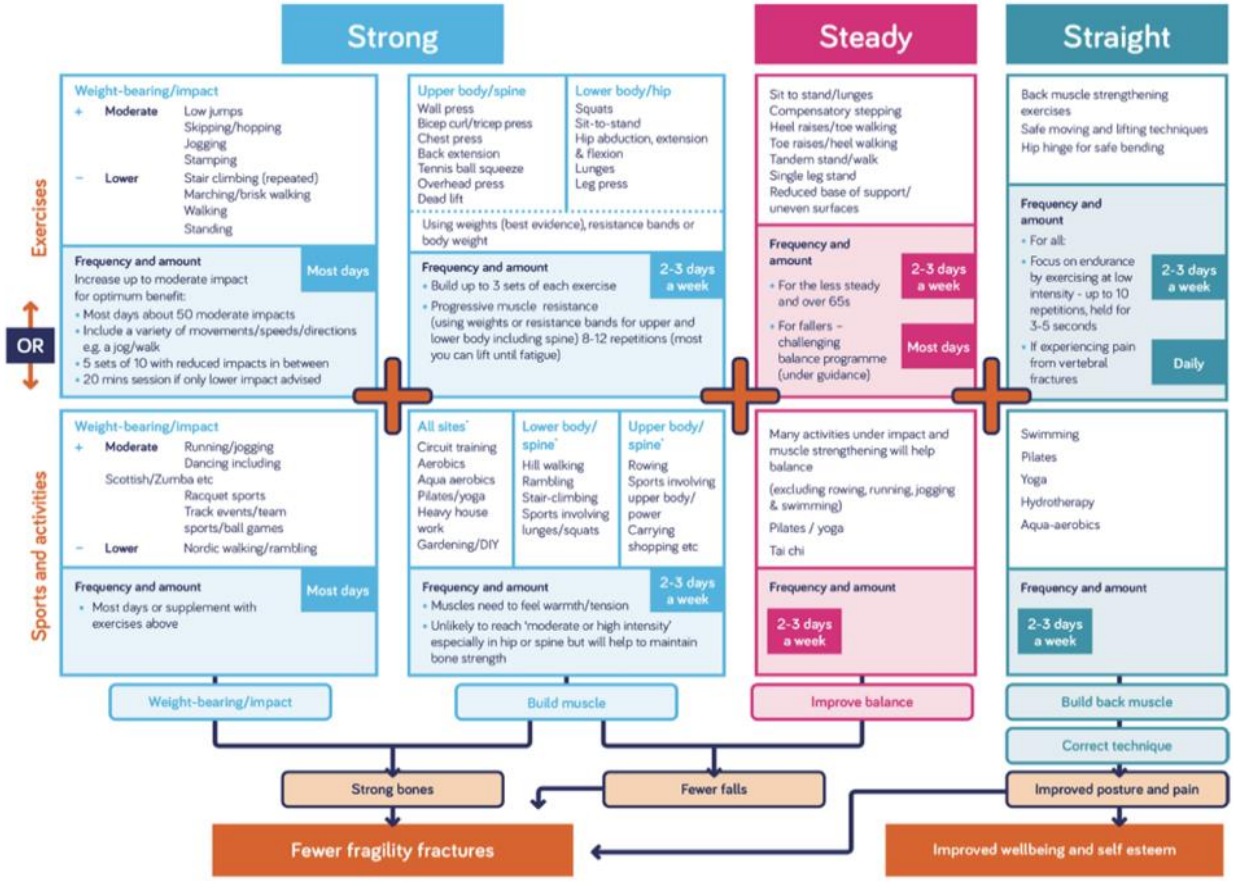

Figure 1. Summary of exercise recommendations5

gardening, and carrying shopping, while avoiding repeated or end-range flexion.

Weight-bearing/impact activities are recommended to be performed at moderate impact, such as jumping, skipping, hopping, and running, with approximately 50 moderate impacts interspersed with rest pauses on most days. However, sports and activities such as running, jumping, aerobics, dancing, and many ball games and sports are more feasible for the majority of people compared to structured exercise because they require fewer facilities or equipment.

Individuals with osteoporosis who have vertebral fractures or multiple low trauma fractures have higher fragility and a risk of further fracture. Therefore, it is recommended that these individuals have customized progressive intensity for impact and muscle-strengthening exercises, preferably under supervision, at least at the start of the program. Several variables to be considered in this group are the number of vertebral fractures, symptoms experienced, other medical conditions, level of fitness, and previous experience with moderate impact activity before the fracture. Urinary incontinence may be a barrier to impact exercise, so addressing stress incontinence may be necessary to implement such an exercise program.

For individuals with osteoporosis who are frail and/or less able to exercise, physical activity and exercise should be adapted according to their ability. It is best to increase the intensity gradually, maintaining good posture and technique, while also monitoring progress and adverse effects. Balance and muscle strength training to prevent falls will be needed for confidence and stability before physical activity levels are increased.

Steady: In this part, exercise and physical activity are recommended to prevent falls. For all people with osteoporosis, especially if they are over 65 years old, exercises to improve balance and muscle strength are recommended. Exercise such as Tai Chi, dance, yoga, or Pilates should be conducted at least twice a week. These exercises are also ideally supervised by a health or exercise professional. If the individual with osteoporosis already has a history of falls, they should be referred to a local fall service to have tailored and specific balance and muscle strength exercises supervised by trained health or exercise professionals. This highly challenging intervention should be performed for 3 hours per week over at least 4 months (25 minutes/day or three 1-hour sessions a week). After the intervention, the exercise could be progressed gradually into higher impact exercises such as brisk walking. Exercises to strengthen back muscles (particularly spinal extensors) and improve posture should also be recommended to reduce the fall risk. Most people do not want to be considered frail. Hence, the language used in communication should be simplified to "maintaining independence" or "reducing the risk of fractures" rather than "fall prevention".

Straight: The last recommendation is to reduce the risk of vertebral fracture, improve posture, and manage symptoms of vertebral fracture. The emphasis should be on continuing rather than prohibiting exercise to reduce fear, enhance confidence, and control, since the individuals are unlikely to experience another fracture. The exercises to improve back extensor strength should be repeated 3-5 times and held for 3-5 seconds at least twice a week to improve posture and support the spine. Safe techniques for day-to-day moving and lifting should be introduced: keep the upper back straight, neck in line with the spine, and hips hinged (for safe bending). The movement should be smooth and controlled within a comfortable range. Twisting movements can be performed if they are smooth and comfortable. Abdominal muscles should be engaged during movements. Several movements to avoid are: sustained, repeated, or end-range flexion and excessive back curve (especially with added load). Individuals with good spine flexibility could be motivated to continue the activity as long as they are fit enough.

For individuals with osteoporosis who have vertebral fractures, early moving and lifting are recommended after the pain subsides to reduce fear, maintain mobility, and function. Daily exercises to strengthen back muscles (at lower intensity), reduce muscle spasm and relieve pain, improve flexibility, and promote the best posture should be repeated 3-5 times and held for 3-5 seconds. Referral to health professionals for a tailored approach might be helpful. Yoga and Pilates could be introduced to help with posture and pain through teaching form, alignment, and relaxation. The class could be led by instructors who are familiar with working with older people and who understand appropriate exercise and movement. Several exercises could be added, such as breathing exercises, pelvic floor exercises, and hydrotherapy, as they could improve the quality of life.

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INA-RESPOND Newsletter

THE POWER OF WORDS: EMBRACING PERSON-CENTERED LANGUAGE FOR A HOPEFUL WORLD

By: Aly Diana

Image created using OpenAI's DALL-E, an AI image generation model

Language shapes our beliefs and may influence our behaviors. Language matters. It impacts how we think about ourselves, as individuals within our families and within society. Language is a powerful tool; while some words may make a person feel uplifted or supported, others may make them feel disrespected, stigmatized, or harmed. We should use it as a tool to effect positive change. People living with or at risk of HIV or other diseases/ disabilities might experience stigma and discrimination, and the wrong language perpetuates this. When we use person-centered language, we acknowledge ourselves and others as fellow human beings.

Person-centered language rightfully places individuals ahead of their conditions or disabilities. It recognizes that people are far more than their substance use disorders, mental health challenges, or physical limitations. This approach to language is about honoring the dignity, worth, and unique attributes of each person. The terms we use are intrinsically linked to a person's identity and self-perception, making it crucial to prioritize the individual rather than the condition. Emphasizing person-first language shifts our focus towards each person's unique journey of recovery and their individual strengths, encouraging a deeper connection that transcends their health status.

There is growing concern about person-centered language or putting people first. When we submit an abstract for a conference or a paper in a journal, some require the usage of person-centered language; they also provide guidelines on words that may or may not be used. In practice and

health facilities, the same encouragement is applied, whether we realize it or not. As educators, we also need to impart this concern to our students.

It feels somewhat abstract and arbitrary when we think about substituting one word for another, for example: replacing 'HIV patient' or 'HIV-infected patient' with 'people living with HIV', or 'diabetic' with 'people living with diabetes'. This change has a deeper meaning and may either cause or prevent stigma or discrimination, impacting perception. I think a better approach is to use an example. Consider two descriptions:

- Jane Doe is labeled as a diabetic, struggles with her sugar levels due to a love for sweets, and faces criticism for her eating habits and non-compliance with insulin therapy.
- Jane Dear is described as a person living with diabetes who encounters challenges in managing her blood sugar levels, partly due to a fondness for sweets. She actively seeks strategies to better manage her condition and adhere to her treatment plan.

The question arises: With whom do you empathize more, Jane Doe or Jane Dear? As a patient, how would you prefer to be described?

Therefore, when a practitioner, researcher, educator, or individual uses deficit-based language filtered through a diagnostic label, they may become negatively biased and depersonalize the individual they are working with or talking about. We sometimes use casual labels when describing individuals, such as ‘junkie’ for an individual with a history of substance use or ‘cutter’ for an individual who engages in self-harm. Typically, when we use certain words, we are not trying to make anyone feel bad. But, if we keep using this kind of language, it can become a normal part of how everyone talks. This means that even without meaning to, the way we talk can start to make people feel less respected or valued. It's important for us to think carefully about the words we choose, so we can maintain a respectful and caring environment. Narrow and negative labels are stigmatizing and can result in discriminatory and ineffective care.

Hopefully, this brief explanation may shed some light on why person-centered language is important. Initially, the shift may seem like mere compliance with guidelines. However, understanding the profound impact of our word choices can transform this action into a meaningful contribution toward creating a more hopeful and respectful world.

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