INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

January 2025

HEALTH POLICY AGENCY

MINISTRY OF HEALTH REPUBLIC OF INDONESIA

2025

INA-RESPOND newsletter

EDITOR-IN-CHIEF

M. Karyana

EXECUTIVE EDITOR

Herman Kosasih

CREATIVE DIRECTOR

Dedy Hidayat

ART DIRECTOR

Antonius Pradana

SENIOR WRITERS

Adhella Menur, Aly Diana

REVIEWERS & CONTRIBUTING WRITERS

Adhella Menur, I Wayan Adi Pranata, Lois E. Bang, Maria Lestari, Melinda Seti-yaningrum, Mila Erastuti, Nurhayati, Nur Latifah Hanum, Restu Amalia, Riza Danu Dewantara, Wahyu Nawang Wulan

THANK YOU

INA-RESPOND Network & Partners

INA-RESPOND Secretariat

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

MASTHEAD

content

January 2025 Edition | issue #136

FEATURES

STUDY UPDATES

InVITE & PROACTIVE

By: Cintya Naya Danastri, Ivana Yulian Hendarsin, Lois E. Bang, Eka Windari R., Nur Latifah Hanum, Restu Amalia Mukti

InVITE

***Figure 1**. Tangerang Hospital*

Preparation for the Site Closeout Visit (SCV) has been completed for all sites. The Site Regulatory Binder and Source Document Worksheet have been stored with the archiving vendor, Indo Arsip. Study documents, such as the final Authorized Signature and Delegation Log (ASDL) and Site Visit Log, will be archived after the SCV, which is expected to take place in February 2025. The next shipment will be conducted for the extracted RNA from the mid-turbinate swabs.

The remaining research assistants (RAs) for the InVITE study were from Site 01 (Tangerang Hospital, Tangerang, Banten): dr. Cintya Naya Danastri and dr. Ivana Yulian Hendarsin. Their dedication as INA-RESPOND-Warm Based RAs is evident through their contributions over nearly 3.5 years. **The Secretariat extends sincere gratitude to them for their spirit and enthusiasm, which were instrumental in the study's success.**

Tangerang Site stands out as the backbone of the study among other sites, recognized for its experienced team and supportive research environment. The site is integrated with the INA-RESPOND Reference Laboratory, led by dr. Dewi Lokida, Sp.PK (K), who contributed to the development of the InVITE Global protocol and diligently oversaw the study. As a respected clinical pathologist and researcher, she maintains strong relationships with all stakeholders involved in the study. Additionally, the ethical approval for the InVITE study was obtained from the Tangerang Hospital Ethical Committee. In this edition, dr. Naya and dr. Ivana share their experiences as RAs at Site 01 over the past 3.5 years.

As the first established site for the InVITE study, Site 01 (Tangerang Hospital) collaborated with two satellite sites—Kelapa Dua Puskesmas (Primary Health Care) and Bojong Nangka

Figure 2. Site 01 study teams (left to right): Evi Herawati, S.ST (LT), dr. Cintya Naya Danastri (RA), Oriza Hamidiah Hariawati, Amd.Ak (LT), dr. Atindriya Tri Iswari (RA), Siti Nufus Eliyati, Amd.Ak (LT), Arif Muflikhun (RA), dr. Ivana Yulian Hendarsin (RA), dr. Amanda Samurti Pertiwi (RA), dr. Dewi Lokida, Sp.PK(K) (PI), dr. Hilwani (Co.PI)

Puskesmas—to boost enrollment and diversify vaccine types and target populations, including people living with HIV (PLWH). dr. Dewi Lokida as the Principal Investigator (PI), with dr. Hilwani as the Co-PI, overseeing COVID-19 vaccination schedules at Tangerang Hospital. Laboratory Technicians (LTs) supporting the hospital site were Evi Herawati, Oriza Hamidiah Hariawati, and Siti Nufus Eliyati. The study teams at the satellite sites comprised Co-PIs who also served as Puskesmas heads (dr. Salmawati, MM, at Bojong Nangka and drg. Rr. Truly Kartikawatie at Kelapa Dua), LTs responsible for sample collection (Rosidah at Bojong Nangka and Marini at Kelapa Dua), and Study Nurses who assisted with enrollment and follow-up (Endang Sri Rahayu at Bojong Nangka and Endang Lina at Kelapa Dua).

Due to the high workload during the early period of the study, dr. Ivana and dr. Naya were supported by three additional RAs: dr. Amanda Samurti Pertiwi and dr. Atindriya Tri Iswari from the INA-PROACTIVE study, and Arief Muflikhun. Arief completed his role on September 1, 2022, followed by dr. Amanda on January 31, 2023, and dr. Atin on August 31, 2023.

Collaboration with satellite sites significantly increased the complexity of enrollment and follow-up processes compared to other studies in a single site. Fortunately, these challenges were successfully managed through effective coordination between the study teams at Tangerang Hospital and Puskesmas. This collaboration began during the study preparation phase, which involved stocking laboratory supplies, preparing enrollment locations, collecting samples, and ensuring proper sample storage and shipment from the satellite sites to Site 01.

Since the InVITE enrollment relied on individuals receiving COVID-19 vaccinations, there was an initial rush to ensure the team seized the opportunity provided by the National Program for Moderna booster vaccinations for health workers, which began on August 18, 2021. The team faced challenges, including the unavailability of some study supplies during the early enrolment period, which required them to be adaptable. The Site 01 study team divided tasks during enrollment to manage the tight preparation timeline. The first enrollment at Bojong Nangka Puskesmas was conducted by dr. Ivana and dr. Naya, with blood collection handled by the Puskesmas LTs. Meanwhile, dr. Amanda, dr. Atin, and Arief prepared the equipment and documentation for the next enrollment at the hospital, assisted by Mrs. Evi, the LT.

Figure 3. Subject enrollment and blood collection process in satellite sites

Figure 4. Study teams at Bojong Nangka Puskesmas, dr. Salmawati (Co-PI) (fourth from the left) Endang Sri Rahayu (SN) (sixth from the left)

Figure 5. Study teams at Kelapa Dua Puskesmas (left to right) Endang Lina (SN), drg. Truly Kartikawatie (Co-PI), Marini (LT)

The screening and informed consent process was challenging due to the large number of people arriving for vaccination, but thankfully, most participants were cooperative. At one point, the study teams successfully enrolled 69 subjects in a single day. Recruitment at the satellite sites presented additional challenges. Some participants lived far from the sites, leading to missed follow-up visits. Some participants were reluctant to comply with study procedures due to fears about blood collection or concerns over the volume of blood being taken.

During the study, RAs conducted biweekly contact with participants to inquire about COVID-19 symptoms over the past 14 days, aiming to capture breakthrough infections. If symptoms were reported, participants were advised to attend an additional visit called the Symptomatic Visit for COVID-19 testing. These biweekly contacts and Symptomatic Visits were memorable for them due to the unique challenges of reaching participants. These challenges included participants sharing a single phone among family members, frequently changing phone numbers, or feeling annoyed by repeated calls despite being informed about the biweekly contact process during consent. Some participants refused to attend the Symptomatic Visit for various reasons, the most common being fear of testing positive for COVID-19 and facing

Figure 6. NIAID visit satellite site (Bojong Nangka Puskesmas)

quarantine, which could disrupt their work. Other reasons included relocating for work or personal matters, making attendance impossible. Despite these obstacles, the RAs did their best to maintain contact with participants through WhatsApp, SMS, or phone calls to monitor their health. While some participants declined the Symptomatic Visit, others were cooperative and eager to share updates about their condition. These individuals prioritized their health and appreciated the free COVID-19 testing, including nasal swabs and blood collection. They also valued receiving their COVID-19 antibody results, which reassured them about the positive impact of the vaccines on their immunity.

On December 5, 2022, Site 01 had the honor of hosting a visit from representatives of the US-NIAID (Renee Ridzon) and Leidos (Jackie Perodin), who were responsible for overseeing the InVITE study. During their visit, they toured Tangerang Hospital and Bojong Nangka Puskesmas. At Bojong Nangka Puskesmas, with the participant's consent, they observed the follow-up process and held discussions with the Puskesmas team, including representatives from Kelapa Dua Puskesmas. They also observed the follow-up process at the hospital and reviewed source document worksheets and case report forms to identify and address any issues related to the study's implementation.

Figure 7. Sample processing at Site 01

dr. Naya and dr. Ivana expressed their gratitude for the opportunity to participate in the InVITE study, which enabled them to broaden their knowledge of international studies, gain the latest insights on COVID-19, and collaborate with experienced researchers. Reflecting on their experiences, they hope that future studies will prioritize more thorough preparation in logistics, site readiness, and coordination to minimize challenges and improve anticipation of potential issues.

The InVITE study at Site 01 was a success, providing valuable insights to the INA-RESPOND Secretariat. **Site 01 stands as clear evidence that long-term collaboration, a dedicated team, and a supportive environment led to smooth research operations.** We greatly appreciate the Site

01 team's outstanding efforts in achieving the highest participant enrollment numbers for the InVITE study in Indonesia. **Despite the high workload and occasional misunderstandings, we are grateful for the team's effective communication and resolution skills.** We were particularly impressed by the RAs' professionalism and comprehensive explanations during our visit with the US-NIAID team. **We look forward to collaborating with Tangerang Hospital on future INA-RESPOND projects and wish the entire Site 01 team continued success.**

INA104

The current phase of the INA-PROACTIVE (A Prospective Observational Cohort Study on HIV Infection and Risk-Related Coinfections/ Comorbidities in Indonesia) study involves data analysis, discussions, and the implementation of manuscript writing based on the concept plans submitted by INA-PROACTIVE study teams. On December 13, 2024, the INA-PROACTIVE team received exciting news: the acceptance of their first manuscript in the *BMC Infectious Diseases* journal, titled **"A Prospective Observational Cohort Study of HIV Infection in Indonesia: Baseline Characteristics and One-Year Mortality."** This manuscript provides a baseline description of the INA-PROACTIVE cohort, outlines the study methods, and identifies risk factors for one-year mortality. Subsequent manuscripts are expected to build upon this foundational work.

HIV/AIDS in Indonesia has seen significant progress since the first case was identified in 1987. National efforts have successfully reduced annual HIV incidence by 50%, from 21 per 100,000 in 2011 to 10 per 100,000 in 2021. However, the epidemic has still caused approximately 372,000 deaths and left an estimated 543,100 people living with HIV (PLWH). Achieving long-term favorable outcomes for PLWH in Indonesia remains a challenge. Despite free antiretroviral therapy (ART) and universal health coverage for CD4 testing, ART access and retention are uneven due to the country's decentralized healthcare system. Viral load (VL) testing is also limited, with only 27% of PLWH on ART receiving VL testing as of January 2023, of whom 91% achieved viral suppression. Nevertheless, UNAIDS estimates overall viral suppression nationwide to be just 14%. The updated longitudinal data on PLWH in Indonesia will be vital in informing clinicians and health policymakers.

This first manuscript describes the INA-PROACTIVE study, a large HIV study conducted by INA-RESPOND from 2018 to 2020 at 19 hospitals across eight major islands in Indonesia. Eligible participants were adults (≥18 years) with HIV who adhered to study protocols; exclusions included plans to relocate or prior imprisonment. Partici-

Figure 1. *Timeline of Manuscript Submission and Acceptance.*

Figure 2. *Map of INA-PROACTIVE study sites.*

pants completed baseline and six-monthly assessments over three years, including demographic data, medical history, and blood tests for CD4+, HIV VL, HBV, HCV, and syphilis. ART regimens followed national guidelines, with virological failure defined as VL >1,000 copies/mL and undetectable VL as ≤50 copies/mL. Opportunistic infections and comorbidities were managed locally, while deaths were recorded and reviewed for AIDS-related mortality.

The analysis in the manuscript focused on one-year outcomes, including virological, immunological, and all-cause mortality. Risk factors for mortality were analyzed, encompassing demographics (e.g., age, gender, region), clinical characteristics (e.g., HIV transmission route, VL, CD4+, BMI, ART type/duration), and ART regimens categorized by treatment line. Survival analysis was conducted using Kaplan-Meier curves to compare survival across VL groups at enrollment. Univariable Cox regression was performed for each potential risk factor individually, followed by multivariable Cox regression to assess all potential mortality risk factors.

The study enrolled 4,336 HIV-infected outpatients. One participant withdrew, and six were excluded due to confirmed negative HIV status, resulting in 4,329 participants. Of these, 4,139 were adults, with 89 missing 6- and 12-month follow-ups, leaving 4,050 participants for the one-year survival analysis.

A total of 4,050 PLWH were included in the analysis, of whom 31.2% were women, with a median age of 35 years (Q1: 29, Q3: 41). Most infections were sexually acquired (53.5% heterosexual, 34.6% MSM). At diagnosis, nearly 56% of participants presented with advanced HIV (WHO stage III-IV), and while most had been on ART for over a year

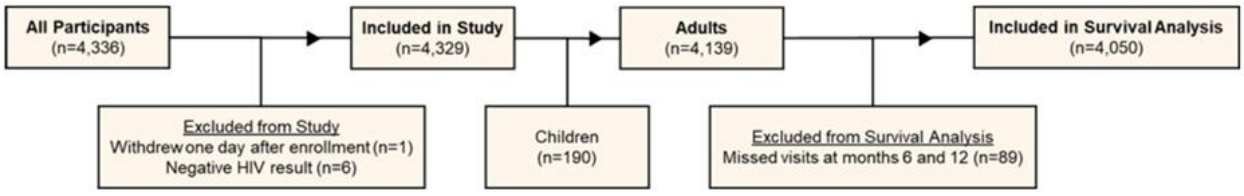


Figure 3. *STROBE diagram of patient selection for analysis.*

at enrollment, 47% still had CD4+ counts <350 cells/μL. At enrollment, 92.1% were on ART (66.9% on efavirenz-based regimens), with 72.4% achieving undetectable VL. After one year, viral suppression increased to 88.8% (3,282/3,694) and to 91.6% (2,328/2,542) among those on ART for more than 12 months. Survival by VL group at enrollment is illustrated in Figure 4, showing a Kaplan-Meier curve indicating decreasing survival with higher VL categories.

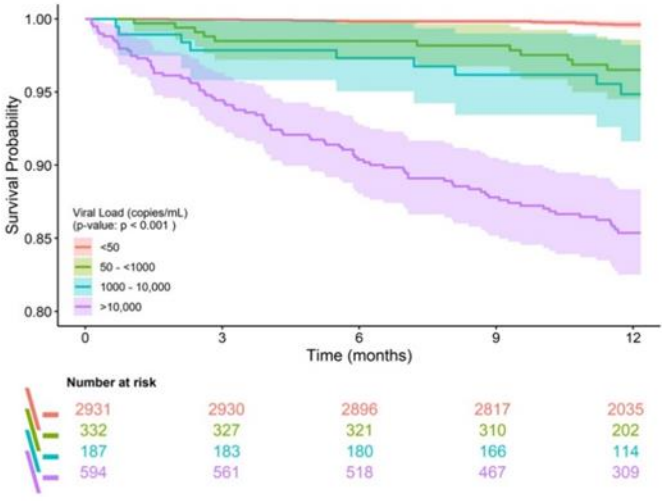
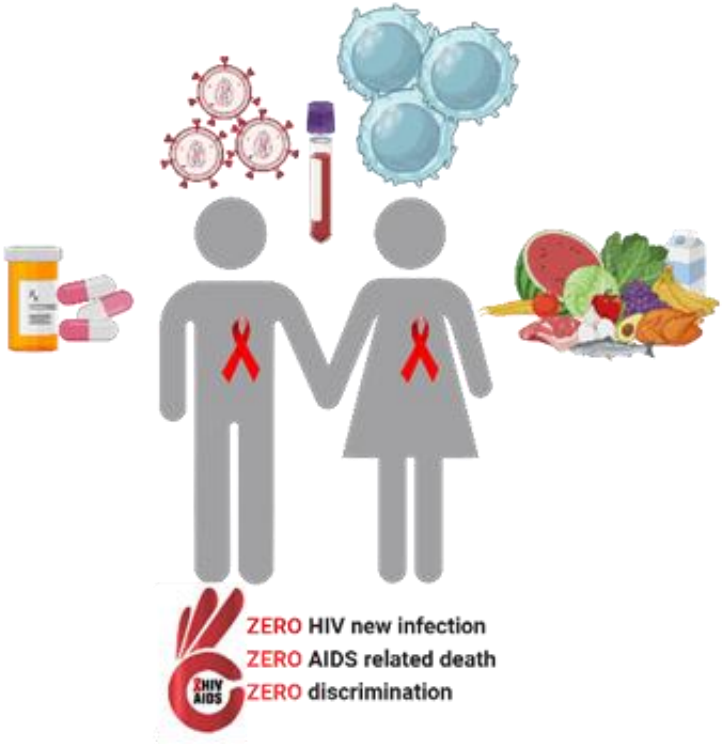


Figure 4 *Kaplan-Meier plot comparing all-cause mortality over one year among study participants grouped by HIV viral load category.*

Among the 115 deaths in the first year, 103 (89%) occurred in participants with detectable viremia at baseline, while 11 (1%) were in those with undetectable viremia. The median CD4+ counts at death were 38 cells/μL for ART-naïve participants and 59 cells/μL for ART-experienced participants. Of the 36 deaths among ART-naïve participants, 30 (83.3%) occurred within the first six months, despite 24 (80%) starting ART within one month and 27 (90%) within three months. Most deaths were AIDS-related: 33 (91.7%) among ART-naïve participants and 66 (83.5%) among ART-experienced participants. **The leading comorbidities contributing to death included tuberculosis (34.3%), multiple infections (25.3%), pneumonia (16.2%), and toxoplasmosis (10.1%).** Multivariable analysis identified **significant mortality risk factors: being aged 40–49 years (adjusted hazard ratio [aHR] 2.19, 95% CI: 1.23–3.97, compared to age 18–29), being underweight (aHR 1.84, 95% CI: 1.18–2.85), having a CD4+ count <200 cells/μL at enrollment (aHR 8.02, 95% CI: 2.69–23.86), and having detectable VL at enrollment (with increasing aHR across higher VL categories compared to undetectable).**

Suboptimal viral suppression rates, even after one year of observation, remained below the UNAIDS 95% target, underscoring the need for improved HIV testing, treatment, and monitoring. Barriers include limited VL testing and delayed ART initiation, particularly in resource-limited settings. The study's observed one-year mortality rate (2.8%) was lower than the national estimate for 2022 (4.8%). This difference may be due to most study sites being referral hospitals with advanced care, a survival bias from 66.1% of participants being ART-experienced for over a year, and the provision of closer follow-up and VL testing during the study.

Key baseline risk factors for one-year mortality included detectable viremia, CD4+ counts <200 cells/μL, and underweight BMI. High VL indicated active HIV replication, systemic inflammation, and accelerated progression to AIDS and death. In advanced HIV, incomplete CD4+ reconstitution increases vulnerability to opportunistic infections such as tuberculosis, pneumonia, and toxoplasmosis, which were leading causes of death in the cohort. Additionally, underweight BMI was independently linked to mortality, suggesting underlying physiological risks beyond its modest correlation with CD4+ count. Previous research has indicated that in PLWH initiating ART, lower baseline



BMI is associated with poorer viral suppression during follow-up, while higher baseline BMI is linked to improved immune reconstitution.

The limitations of this study include the lack of assessment of other factors influencing mortality outcomes, such as socioeconomic status, mental health, social support, health literacy, and medication adherence. Additionally, the study population may not represent the general PLWH population in Indonesia, as it focused on large referral hospitals, which may attract participants with advanced disease but also provide better care. Furthermore, incarcerated individuals, an important PLWH population in Indonesia, were not included.

In conclusion, the INA-PROACTIVE study provides the largest nationwide observational data on PLWH in Indonesia to date. Findings from the first year of observation **emphasize the critical importance of early diagnosis, early treatment, and routine monitoring of VL and CD4+ cell counts.** Incorporating routine VL testing alongside CD4+ monitoring into the national treatment program should be considered, as it can improve decision-making, reduce mortality, and enhance treatment outcomes.

Hopefully, this first publication from INA-PROACTIVE will serve as a valuable reference for HIV management in Indonesia and globally. Additionally, it can act as a driving force for the further dissemination of INA-PROACTIVE data.

REPORT

MESSAGES FROM OUR NSC MEMBERS: PAVING THE WAY FOR INA-RESPOND'S FUTURE

By: INA-RESPOND NSC Members and Secretariat

New Year, New Hope! To move forward with strength, we must first reflect on the journey that has brought us here. Over the past 14 years, INA-RESPOND has grown into a center of excellence in infectious disease research in Indonesia. This achievement would not have been possible without the extraordinary dedication and contributions of our Network Steering Committee (NSC) members. During the pivotal time of INA-RESPOND's establishment, these individuals were like rare diamonds—respected academics and clinical researchers selected for their exceptional research performance. Established in 2010, the NSC comprises representatives from participating hospitals, institutions, and the US-NIAID. This committee has played a vital role in the day-to-day governance of the network, including planning activities, developing research protocols, approving projects, monitoring progress, and fostering new partnerships. We are deeply grateful for their warmth and open-mindedness in welcoming INA-RESPOND as a new infant in Indonesia's research landscape. In this New Year edition, we share insights from our conversations with NSC members about their hopes and vision for the future of INA-RESPOND.

Opening the conversation, they reflect on how clinical research culture in Indonesia has historically lagged behind, with only a handful of hospitals—primarily teaching hospitals—actively engaging in research, particularly operational studies, to improve clinical services. Similarly, only a small number of universities in Indonesia are classified as research universities, despite the mandate for all universities to uphold the Tri Dharma Perguruan Tinggi—Education, Research, and Community Service. Consequently, access to evidence-based medical services in Indonesia has remained limited. With the tremendous enthusiasm of the late Minister of Health, dr. Endang Sedyaningsih, the US-NIAID team led by Dr. Cliff Lane and Dr. Sophia Siddiqui, and the dedication of the former National Institute of Health Research and Development, led by dr. Trihono with support from dr. Siswanto and dr. M. Karyana, they built the network of research sites from scratch.

Establishing these sites was no easy task. Finding individuals who are genuinely interested in research, inspiring them to join, work at the sites, and commit to responsible networking has been the result of their relentless efforts. Beginning with meticulous efforts on observational studies of febrile patients, research capacity across medical faculties and hospitals was gradually enhanced. Many clinical doctors, particularly those managing infectious diseases, were involved from the early stages of proposal development, research ethics training, and conducting proper clinical research, to publishing in international journals and managing repositories for clinical specimens.

This remarkable spirit, combined with substantial funding, has facilitated the establishment of re-

search sites equipped with the necessary infrastructure and dedicated teams to conduct impactful clinical research on infectious diseases. They are confident that INA-RESPOND has played a pivotal role in advancing our understanding of various critical areas, including the causes of fever, sepsis, tuberculosis, cysticercosis, pediatric pneumonia, and HIV. Today, they are proud to say they have a team of skilled researchers who are well-equipped and prepared to conduct rapid -response studies at 19 sites across Indonesia. This network proved its immense value during the COVID-19 pandemic by swiftly supporting government efforts through research essential for effective pandemic management. Over the past decade, INA-RESPOND's initiatives have significantly advanced progress in epidemiology, diagnostics, immunology, molecular biology, and clinical management.

As the saying goes, **"Tall trees catch the most wind."** Similarly, INA-RESPOND has faced considerable challenges. During the COVID-19 pandemic, research activities were undeniably disrupted by the demands of managing COVID-19 in hospitals and the restrictions on the mobility of researchers and study participants. Additionally, the dissolution of the NIHRD and its replacement with the Health Development Policy Agency required INA-RESPOND to adapt, leading to a temporary halt in research activities. Over time, they have also witnessed the departure of some researchers, whether due to passing away, relocating, or retiring. They emphasized the importance of nurturing young researchers at the sites who are genuinely passionate about pursuing a research career, rather than viewing the role of research assistant merely as a stepping stone to specialization. However, they acknowledged the challenge of retaining research assistants, as INA-RESPOND currently lacks a defined career path for these roles.

As we step into 2025, INA-RESPOND is ready to embrace new challenges and seize fresh opportunities. The NSC members have outlined several key priorities for the future:

- Strengthening Local Research Capacity

  Continued investment in training for local researchers and clinicians is essential. By enhancing skills in epidemiology, biostatistics, and cutting-edge laboratory techniques such as sequencing, INA-RESPOND can empower researchers to tackle Indonesia's most pressing health challenges.
- Ensuring Sustainable Funding

  To maintain momentum, the network must secure sustainable funding from diverse sources, including international donors, private-sector partnerships, and national budgets.
- Advancing Diagnostic Technology

  Collaboration with international institutions to develop affordable and accurate diagnostic tools will be critical in detecting pathogens, including antimicrobial-resistant microorganisms, early.
- Pandemic Preparedness

  Collaborate with Clinical Research Units (CRUs) to respond to infectious disease outbreaks quickly and efficiently. Support the development of new vaccines and therapies to address potential pandemics.
- Expanding Research Scope

  While infectious diseases remain a priority, there is growing interest in broadening research to include non-communicable diseases, such as degenerative conditions and diseases caused by environmental pollution.
- Operational Research and Advocacy

  INA-RESPOND aims to support government programs through operational research that provides evidence-based recommendations tailored to Indonesia’s unique health challenges.

The NSC members envision INA-RESPOND as a driving force not only for research but also for advocacy and policy development. With its focus on innovation, collaboration, and strengthening local capacity, INA-RESPOND serves as a model of how a national initiative can achieve a global impact in combating infectious diseases.

As INA-RESPOND transitions to a new phase, they hope we can draw inspiration from the unwavering spirit and extraordinary efforts of everyone involved, laying a strong foundation for its future. The network's journey demonstrates that establishing research sites capable of functioning as effectively as they do today requires time, dedication, and perseverance. Their message to us is clear: moving forward, we must prioritize cohesive, healthy, and supportive site teams, along with a strong secretariat and laboratory infrastructure. Continued collaboration with US-NIAID and the Ministry of Health will be essential. This synergy will empower us to conduct high-quality research that addresses the infectious disease challenges faced by both Indonesia and the global community. From its humble beginnings to its current stature as a shining example in clinical research, INA-RESPOND stands as a beacon of hope for Indonesia and the world.

"As we gathered their stories and insights, we found tears welling in our eyes. Today, we walk confidently along the path paved by our NSC members, building the great reputation of this infectious disease research network. Hopefully, we can continue to do our best in the future, creating new milestones with their guidance. A big thank you to our NSC members!"

Pratiwi Sudarmono, Prof., Dr., PhD, Sp.MK(K)

INA-RESPOND should be a model for advancing and continuously strengthening the medical research ecosystem in Indonesia, while ensuring the provision of evidence-based medical care for patients.

Ketut Tuti Parwati Merati, Prof., DR., dr., Sp.PD-KPTI, FINASIM

As researchers, it is our responsibility to ensure that the specimens we have collected are utilized effectively. These 'treasures' in our specimen repository hold immense value, and we must make the most of this invaluable resource through meaningful studies.

Usman Hadi, Prof., dr., PhD., Sp.PD, KPTI-FINASIM

INA-RESPOND has great potential to become a leading center for infectious disease research and collaboration. We must play an active role in addressing global challenges such as antimicrobial resistance, emerging pandemics, and endemic diseases.

Muhammad Hussein Gasem, Prof., dr., Sp.PD-KPTI, PhD

I hope INA-RESPOND will continue to thrive by expanding its scope and increasing its network of hospitals as clinical research sites for both infectious and non-infectious diseases, including cancer, genomics, and AI-based research.

Mansyur Arief, Prof., dr., Sp.PK(K), PhD

I hope this collaboration will accelerate the achievement of the health transformation goals set by the MoH, particularly in addressing infectious diseases in Indonesia. The NSC is expected to maintain a platform and opportunities to actively contribute to formulating policies and research strategies.

Dewi Lokida, dr., SpPK(K)

Drawing from our experiences over the past decade, INA-RESPOND must have active, dedicated researchers who stay current in their fields, both at the National Steering Committee and at the sites.

Erlina Burhan, Prof., DR., dr., MSc, Sp.P(K)

In the future, there is great potential to expand the number of clinical trials conducted. Currently, 16 new TB vaccines are in the pipeline at various stages of development, and I hope some of these vaccines can be studied under the umbrella of INA-RESPOND.

Bachti Alisjahbana, Prof., dr., Sp.PD-KPTI, PhD

INA-RESPOND should continue to grow for two main reasons. First, Indonesia's tropical location makes it highly vulnerable to infectious diseases. Second, its scientists, physicians, and the MoH are eager to contribute to managing these infections. I hope INA-RESPOND can lead vital research, helping Indonesia combat infectious diseases and gain international recognition.

Abu Tholib Aman, Dr., MSc, PhD, Sp.MK(K)

I hope INA-RESPOND continues to thrive as a unique research network with strong systems and sustainable collaboration. I also hope we remain proactive in monitoring and addressing emerging threats from novel pathogens capable of causing deadly pandemics.

Vivi Setiawaty, Dr.,dr.,M.Biomed

I hope INA-RESPOND can empower local researchers by providing them with the skills to analyze clinical, epidemiological, laboratory, and bioinformatics data

We, as NSC members, are committed to continuing our contributions to INA-RESPOND. We would also like to express our sincere appreciation to the NSC lead, dr. M. Karyana, for his steadfast dedication to INA-RESPOND despite the challenges faced.

REPORT

BUILDING THE FUTURE: INA-RESPOND IN 2025

By: Aaron Neal

Dr. Aaron Neal
NIAID Lead for the Indonesia Research Partnership

INA-RESPOND has much to celebrate over the past year, and much to be excited for in 2025. Highlights from 2024 include the completion of the InVITE study, presentations at the annual RePORT tuberculosis (TB) meeting in Brazil, and the acceptance of key publications from HIV study (INA-PROACTIVE) and TB study (TRIPOD). Despite the successes from last year and the many years before, it is important to acknowledge the uncertainty that has hovered around the future direction of the partnership. This year will bring substantial changes to many elements of INA-RESPOND, but I remain optimistic and excited for these new opportunities in 2025.

Beginning with the establishment of Indonesia National Research and Innovation Agency (BRIN) in 2019 and continuing through the Ministry of Health (MoH) decree HK.01.07/MENKES/1458/2023 in 2023, the organization of clinical research in the MoH has shifted significantly. INA-RESPOND remains a government-to-government partnership between the MoH and US-NIAID, so we must adapt to this new landscape and ensure that our structure and activities align with MoH expectations. Health Minister Budi Gunadi Sadikin, Director General for Health Services (Yankes) Azhar Jaya, and Dr. Cliff Lane reached the decision to relocate INA-RESPOND from the Health Policy Agency (BKPK) to RSPI Sulianti Saroso (RSPI SS) as a joint Clinical Research Unit (CRU) focused on infectious diseases. This is a significant change in the MoH governing partner, which began as NIHRD, morphed into BKPK, and is now transitioning to Yankes. With Yankes as the new governing partner and RSPI SS as the new operational partner, this will mean physically relocating the Secretariat and staff to RSPI SS, integrating the organization of the partnership into the existing CRU organization, and mapping out ways for INA-RESPOND and RSPI SS to work both independently and in collaboration with each other. This is no simple task, and those who were with INA-RESPOND in the early days will understand the challenges that come with establishing a new partnership. We have already begun planning the transition of INA-RESPOND to

Yankes, and DG Azhar Jaya visited the NIH on 4-5 December to hold the first Executive Steering Committee meeting with Dr. Lane and others from Yankes, RSPI SS, INA-RESPOND, and NIAID. We anticipate additional meetings in Jakarta in early 2025 to finalize elements of the transition.

Though the Secretariat is expected to relocate, its structure, function, and capacity should remain the same. In fact, I expect that there will be greater opportunities for Secretariat staff to share scientific knowledge and operational expertise with MoH CRUs and the INA-CRC, ultimately contributing to enhanced research capacity across the MoH. The INA Reference Laboratory remains a strong component of INA-RESPOND, and I do not anticipate any significant changes to the lab under the new partner. Like the Secretariat, I expect that there will be new opportunities for lab staff to strengthen lab capacity at RSPI SS and other MoH labs through trainings and technical exchanges.

The current INA-RESPOND sites will likely be the most affected by the changes coming to the partnership. Under the new MoH system of CRUs, it makes the most sense for INA-RESPOND to work directly with the newly established CRUs as studies require. This would be different from the current model of core sites staffed by INA-RESPOND research assistants. The logistics of working with CRUs still need to be discussed in detail, but it seems that CRUs now fulfil the role that INA-RESPOND research units once occupied. The final element that will see changes in 2025 is the high-level governance of the partnership. The relocation of INA-RESPOND to RSPI SS brings the expectation of merging organizational and leadership structures. A new governance model has been approved by DG Azhar Jaya and Dr. Lane, and once the remaining elements of the transition have been finalized, we anticipate hosting a partnership-wide meeting to celebrate the past success of INA-RESPOND and kick-off the future of the partnership under Yankes and RSPI SS.

I am most excited about the scientific possibilities for INA-RESPOND in 2025. As we all know, the completion of the InVITE study marked the end of active INA-RESPOND studies. During this down-time, Secretariat and NIAID staff have been seeking new research and funding opportunities that would begin this year. Many of the MoH and global infectious disease priorities are the same as in past years, i.e. HIV/AIDS, TB, COVID-19, and antimicrobial resistance, but we have also seen renewed interest in longstanding disease threats like Dengue and Zika virus infections. I anticipate opportunities to collaborate with RSPI SS investigators on TB research and international investigators on dengue research, including a potential phase III global study on immunomodulatory drugs for severe dengue. These potential studies and others will be excellent opportunities to showcase the growth of INA-RESPOND as the partnership pursues more high-impact interventional studies rather than large-scale surveillance studies.

INA-RESPOND is adapting to significant changes in the Ministry of Health. This will be the most substantial reconfiguration of the partnership since it was established in 2010, and I am excited for future opportunities to conduct important infectious disease research with our new partners Yankes and RSPI Sulianti Saroso.

REPORT

INDONESIAN MOH DELEGATION VISIT TO THE US NATIONAL INSTITUTES OF HEALTH (US NIH)

By: Meity Siahaan, Dedy Hidayat

Left photo: Dr. H. Clifford Lane (left) showing the model of the NIH building to Dr. Nizar Yamanie (middle) and DG Azhar Jaya (right). Right photo: DG Azhar Jaya and Dr. H. Clifford Lane conversing at the end of the visit.

On December 4-5, 2024, a delegation from the Indonesian Ministry of Health (MoH) visited the United States National Institutes of Health (NIH) to strengthen existing collaborations and explore new opportunities in health research. This visit was an important step in strengthening bilateral cooperation in clinical research and capacity building between Indonesia and the United States.

The delegation included high-ranking officials from various departments within the Indonesian MoH. Among the key representatives were Dr. Azhar Jaya, Director General of the Health Services Directorate; Ms. Indri Roosliamiati, Acting Director of BB Binomika; Dr. Nizar Yamanie, a Senior Leader and Neurologist Consultant at RS PON Mahar Mardjono; Dr. Yuli Felistia, Head of the Clinical Research Unit at RS PON Mahar Mardjono; Dr. Vivi Setiawaty, Director of Research at RSPI Sulianti Saroso Hospital; Dr. Maria Lawrencia, Head of the Clinical Research Unit at RSPI Sulianti Saroso Hospital; and Ms. Meity Siahaan, Finance and Administration Manager for INA-RESPOND.

During their two-day visit, the delegation engaged in a series of meetings with NIH leaders and researchers. Among those who met with the Indonesian officials were Dr. Jeanne Marrazzo, Director of the National Institute of Allergy and Infectious Diseases (NIAID); Dr. H. Clifford Lane, Deputy Director of NIAID; Dr. Avindra Nath, Clinical Director of the Division of Intramural Research; Dr. Richard T. Ben-

son, Director of the Office of Global Health and Health Disparities (OGHHD) in the NINDS Division of Clinical Research; Dr. Sudha Srinivasan, Program Director of OGHHD; and Dr. Kathleen Maletic Neuzil, Director of the Fogarty International Center. These meetings provided an opportunity to discuss mutual research priorities, current projects, and potential areas for future collaboration.

The focus of the visit was the INA-RESPOND partnership, but discussions with NIAID, NINDS, and FIC touched on a range of topics, including vaccine-preventable diseases, tuberculosis research, genomics, ischemic stroke, malnutrition, global clinical research networks, research training exchanges, and more. It also featured a guided tour of NIH facilities. These activities provided valuable insights into NIH's research infrastructure and operational models, which could serve as a reference for enhancing Indonesia's research capabilities. The discussions also emphasized the importance of strengthening global health research partnerships to address pressing health challenges.

One of the main agenda items during the visit was the first Executive Steering Committee (ESC) of the transitioning partnership, which was held on December 5. The meeting began with statements from DG Azhar Jaya and Dr. Lane reaffirming each side's commitment to collaboration and the INA-RESPOND partnership. Following an acknowledgement of the recently signed MoH-HHS Memorandum of Understanding (MoU) and the soon-to-be-signed MoH-NIH Letter of Intent (LoI), the ESC launched into presentations and discussions on the planned transition of INA-RESPOND from BKPK to RSPI Sulianti Saroso Hospital in Jakarta. The move is expected to align INA-RESPOND's activities with the broader goals of the Indonesian MoH. The discussion covered the establishment of a Scientific Steering Committee (SSC) to provide strategic guidance, improving financial structures to ensure sustainability, and fostering long-term funding opportunities to support ongoing and future research initiatives.

The delegation and NIH representatives also discussed plans to improve laboratory and research capacity in Indonesia. This initiative aims to strengthen the country's laboratory capabilities, particularly in infectious disease research, enhancing preparedness and response to health emergencies.

The proposed relocation of the INA-RESPOND Secretariat to RSPI Sulianti Saroso Hospital was another significant topic of discussion. Two relocation options were explored: establishing a standalone building, which would require renovation, or utilizing shared space within the hospital. Both options involve cost-sharing arrangements, and further discussions will be held to finalize the best approach.

Looking ahead, a follow-up meeting in Jakarta is scheduled for February 2025. This meeting will focus on finalizing collaboration strategies and operational plans. Preparations for this meeting will include site assessments at RSPI Sulianti Saroso Hospital to evaluate the proposed relocation sites and ensure a smooth transition.

The visit to the NIH reaffirmed the importance of INA-RESPOND's international partnerships, particularly in the field of infectious disease research. It underscored the commitment of both the Indonesian MoH and NIH to addressing global health challenges through collaborative research efforts. The delegation's engagements with NIH leaders and experts strengthened the foundation for future initiatives, ensuring that Indonesia continues to play a leading role in health research on a global scale.

SCIENCE CORNER

A NEW YEAR, NEW HOPE IN THE FIGHT AGAINST HIV WITH LENACAPAVIR —NO CAP!

By: Adhella Menur

As a member of the INA-RESPOND Science team, I am thrilled with the acceptance of the first publication from our HIV study, entitled "***A Prospective Observational Cohort Study of HIV Infection in Indonesia: Baseline Characteristics and One-Year Mortality***" in the BMC Infectious Diseases journal. This paper provides valuable evidence for Indonesia and serves as a foundational reference for future exploratory publications. Reading the paper, it becomes evident that the chain of HIV infection in Indonesia remains far from being broken. The most commonly observed modes of HIV transmission were high-risk sexual activities, including heterosexual and men who have sex with men (MSM), as well as intravenous drug use (IDU). Alarmingly, more than half of the participants were late presenters, meaning they were diagnosed with HIV only after reaching WHO clinical stages III or IV. One year into the observation, we found that the UNAIDS target of 95% viral suppression was not achieved, even though the study was mostly conducted at major referral hospitals in large cities. This highlights significant gaps in early detection, treatment challenges, and outcomes, ultimately resulting in a high risk of ongoing transmission within communities. A recent statement from the Ministry of Health revealed a continuous annual increase in new HIV cases, with the highest prevalence among productive age groups (25–49 years).

Having said that, there is an urgent need for enhanced prevention strategies to curb the HIV epidemic. While HIV vaccines are still under development, optimizing the use of highly efficient and effective Pre-exposure Prophylaxis (PrEP) is critical. **At the end of 2024, the journal Science named Lenacapavir the Breakthrough of the Year**, recognizing its remarkable results as a PrEP option with 96–100% efficacy. Science described it as "a pivotal step toward diminishing HIV/ AIDS as a global health crisis. In this New Year edition, we will explore how Lenacapavir offers new hope to break the chain of HIV transmission—No Cap!

Lenacapavir: the first-in-class, long-acting, multistage capsid inhibitor

Lenacapavir describes how basic science research lays the groundwork for translation into clinical practice. Dr. Wesley Sundquist, a Samuels Professor and chair of biochemistry at the University of Utah, along with his team, dedicated their research to understanding the molecular structure of HIV and its mechanisms for infection and replication. Sundquist's team focused specifically on the HIV capsid protein (p24), a cone structure that encapsulates HIV RNA. This capsid protects the viral RNA and facilitates its transport into the host's nucleus. In fact, the capsid does not immediately fall apart when HIV enters a cell, as previously thought, but remains intact and can even squish through pores in the nuclear membrane to deliver its payload of viral genes. The capsid plays essential roles throughout the HIV replication cycle, and Sundquist's team figured out that disrupting this structure could prevent the virus from assembling properly or entering host cells' nuclei.

These groundbreaking insights inspired the pharmaceutical company Gilead Sciences to explore the development of drugs targeting the HIV capsid, with Sundquist as the consultant.

With the benefit of X-ray crystallography, the team designed Lenacapavir (initially known as GS-6207), which targets a highly conserved capsid interface and exerts multistage, selective inhibition of the HIV capsid. By interfering with capsid-mediated nuclear uptake of pre-integration complexes and impairing virion production, Lenacapavir inhibits viral replication at both early and late stages of the life cycle:

- Inhibits nuclear import: By making the capsid cone rigid, Lenacapavir prevents it from slipping into the nucleus. Additionally, it binds to the same capsid interface utilized by host nuclear import co-factors, such as nucleoporin 153 (Nup153) and cleavage and polyadenylation specificity factor 6 (CPSF6), thereby interfering with the transport of viral complexes to the host nucleus.
- Inhibits capsid uncoating: Lenacapavir stabilizes the capsid shell, preventing its uncoating and thereby halting viral replication during the initial stages of infection.
- Inhibits capsid assembly: Lenacapavir disrupts the capsid lattice during the maturation phase of the virus, rendering newly formed HIV particles non-infectious.

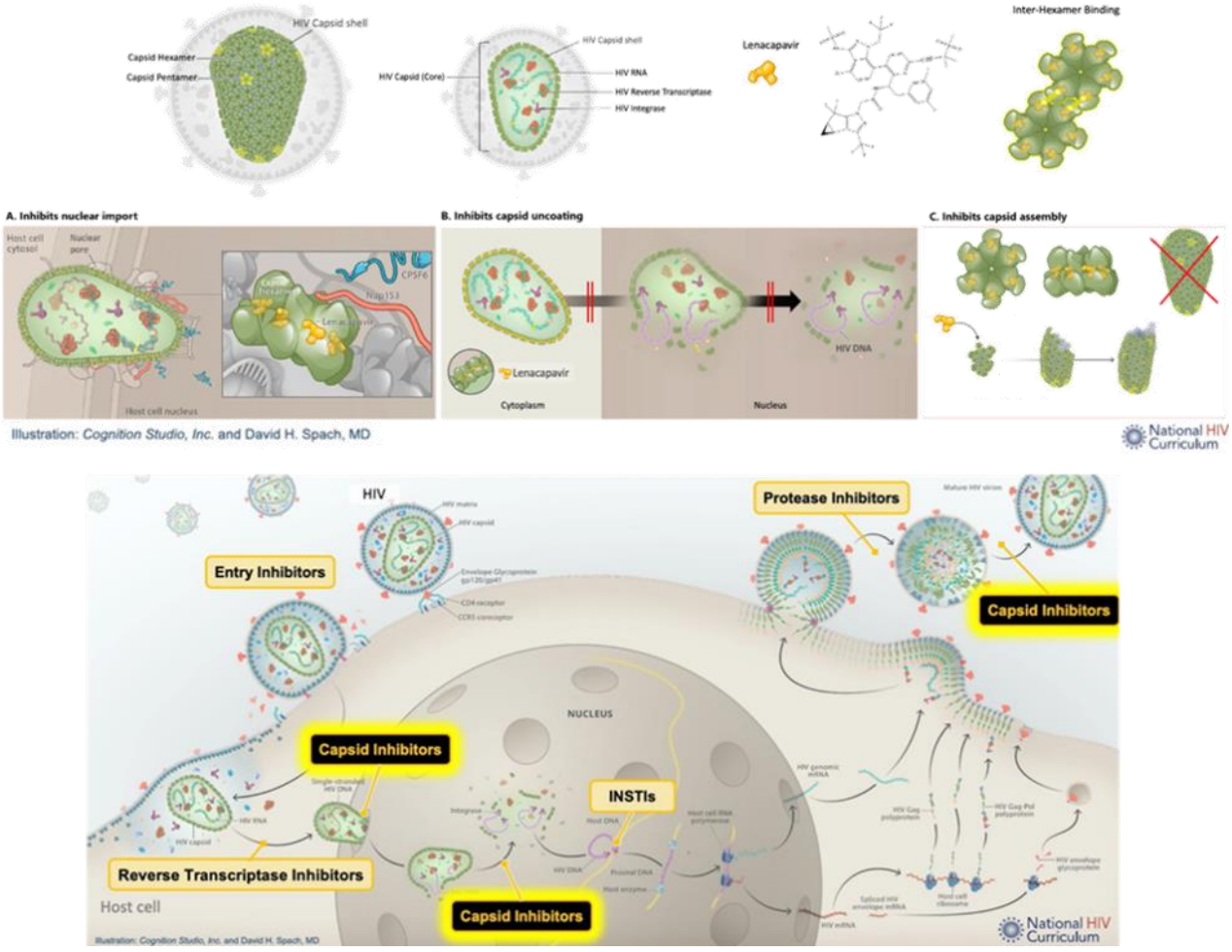


Figure 1. HIV capsid protein and the mechanism of action of Lenacapavir. Source: Highly recommended viewing - Mini-Lecture Series: *HIV Capsid Inhibitors: Mechanism of Action by the National HIV Curriculum*. Available at: https://www.youtube.com/watch?v=iZ9KDxV5Zbs&t=730s

In the development of Lenacapavir, the team also highlighted the importance of a long-acting agent to improve adherence and ensure successful intervention. To maintain effective plasma trough concentrations over an extended period, a long-acting drug must exhibit high potency, a slow and sustained release rate, and a slow systemic elimination rate. Following oral administration, Lenacapavir is unaffected by food intake, has a half-life (t1/2) of 10–12 days, and has an apparent clearance of 55 L/h. With subcutaneous (SC) administration in the abdomen, it demonstrates a significantly longer t1/2 of 8–12 weeks and a lower apparent clearance of 4.2 L/h. A slow initial rise in plasma levels was observed during the first few weeks following SC administration, which led to the consideration of an initial pharmacokinetic loading dose using oral Lenacapavir. The primary route of excretion is through feces, accounting for 76% of all excreted drug, with 33% excreted unchanged, while less than 1% of the drug is eliminated renally. Lenacapavir is thus characterized by low human clearance and low aqueous solubility, which supports its administration every 6 months. The FDA emphasized that the optimal dosing interval is 26 weeks to ensure plasma trough concentrations consistently remain above the minimum drug concentration required to inhibit the virus effectively.

With its novel mechanism of action, Lenacapavir has no overlapping resistance with any approved agents, and no preexisting resistance or polymorphisms have been identified that reduce viral susceptibility to the drug. However, emergent resistance to Lenacapavir was observed in clinical studies, although it was often associated with a high fitness cost to the virus. This indicates that while resistance may develop, it comes at a significant disadvantage to the virus's ability to replicate and survive. Further observation and monitoring are unquestionably needed to fully understand and manage the potential for resistance.

Lenacapavir was approved by the FDA on December 22, 2022, for the treatment of heavily treatment-experienced adults whose current antiretroviral therapy (ART) regimens were failing due to resistance, intolerance, or other safety concerns. The approval was based on results from the Phase 2/3 CAPELLA trial, which evaluated the efficacy and safety of Lenacapavir in combination with an optimized background regimen for patients with multidrug-resistant HIV-1 infection.

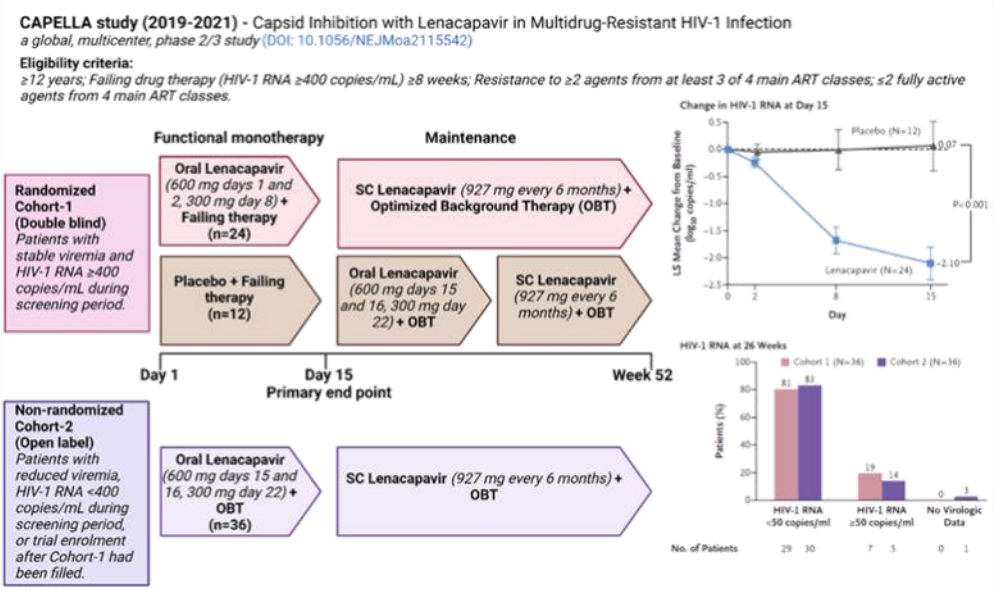


Figure 2. CAPELLA study (Source: Segal-Maurer S et al., 2022, DOI: 10.1056/NEJMoa2115542). OBT/ optimized background therapy: a customized treatment regimen that's used to increase the chances of a new HIV drug succeeding. Created with Biorender.com.

Lenacapavir demonstrated significant efficacy as functional monotherapy, leading to a substantial decrease in viral load. When combined with optimized background therapy, Lenacapavir achieved high rates of virologic suppression and a clinically meaningful increase in CD4+ counts. During the maintenance period, Lenacapavir-associated capsid mutations were observed in 8 patients (4 in Cohort-1 and 4 in Cohort-2). Among these, 6 patients exhibited an M66I mutation (including one with M66I + N74D), while other mutations included Q67H + K70R and K70H. Despite these mutations, some patients maintained viral load suppression while continuing Lenacapavir with minimal or no adjustments to their optimized background therapy.

No serious adverse events related to Lenacapavir were reported. Most adverse events were mild or moderate, with the most common being injection-site reactions. The SC administration of Lenacapavir every 6 months eliminates the need for daily pills, maintaining therapeutic drug levels between visits. This long-acting regimen reduces the uncertainty and variability associated with incomplete adherence, offering a significant advantage for patients.

The PURPOSE-1 & PURPOSE-2 Studies: Groundbreaking evidence supporting Lenacapavir's role in HIV Prevention

PrEP is an amenable strategy to achieve the ambitious UNAIDS target of Zero new HIV infections by 2030. Numerous clinical trials have validated the efficacy and safety of PrEP; however, its success is heavily reliant on adherence, which remains a significant challenge as it requires individuals to make positive health choices consistently. Poor uptake and adherence to daily pill regimens weaken PrEP's effectiveness. To address this, several approaches such as the monthly Dapivirine vaginal ring, bi-monthly intramuscular injections of Cabotegravir, and intravenous infusions of broadly neutralizing antibodies (VRC01) every 8 weeks have been explored. Adding to these strategies, twice-yearly SC injection of Lenacapavir emerges as a promising solution to improve adherence and ensure effective PrEP. "*It has the potential, if we can do it right, which means going big and getting it out there*," says Professor Linda-Gail Bekker, an infectious disease specialist at the University of Cape Town who led PURPOSE-1 study, one of the two Lenacapavir efficacy trials.

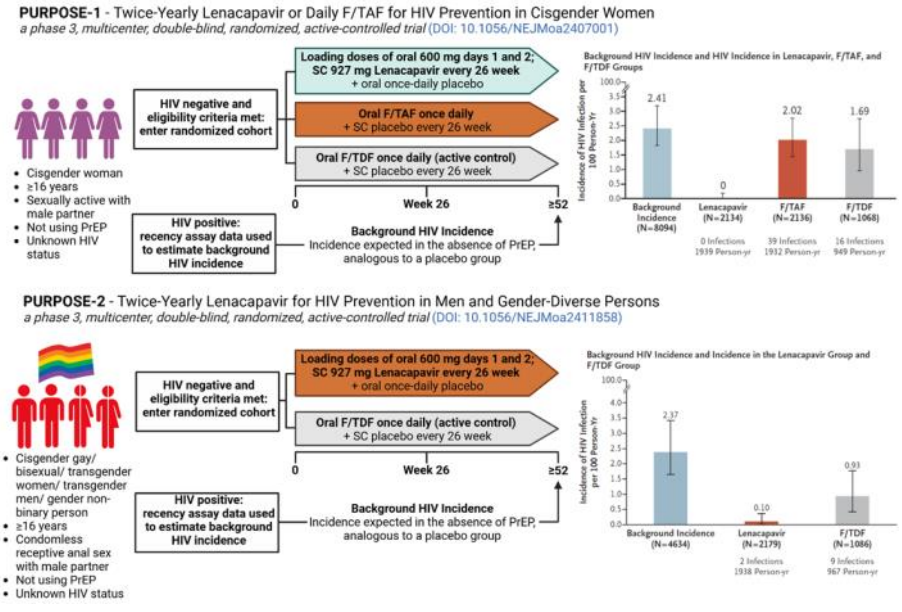


Figure 3. PURPOSE-1 & 2 studies (Source: Bekker LG et al., 2024, DOI: 10.1056/NEJMoa2407001; Kelley CF et al., 2024, DOI: 10.1056/NEJMoa2411858). F/TDF: emtricitabine–tenofovir disoproxil fumarate; F/TAF: emtricitabine–tenofovir alafenamide; cisgender: a gender identity that corresponds to their sex assigned at birth; gay: sexually attracted to people of the same sex or gender; bisexual: sexually attracted to more than one sex or gender; transgender: a gender identity that does not correspond with the sex registered for them at birth; gender non-binary: a gender identity that is not exclusively male or female. Created with Biorender.com.

The PURPOSE-1 study of Lenacapavir delivered astonishing results as HIV PrEP, demonstrating 100% efficacy among adolescent girls and young women in South Africa and Uganda. This was followed by the PURPOSE-2 study results, which showed 96% efficacy among gender-diverse persons who have sex with men in the United States, South Africa, Peru, Brazil, Argentina, Mexico, and Thailand. During the PURPOSE-1 study, there were 193 pregnancies in the Lenacapavir group, with no HIV infections reported. A congenital abnormality, polydactyly, was observed in an infant born to a participant in the Lenacapavir group. However, the investigator determined this abnormality to be unrelated to the drug, as the participant had a strong family history of the condition. In the PURPOSE-2 study, two cases of HIV infection were reported in the Lenacapavir group during the trial period, both associated with the emergence of capsid resistance (N74D mutation) resulting from Lenacapavir monotherapy. While cases of HIV infection despite PrEP use have been documented—often linked to high exposure levels and repeated mucosal injury—more than 99% of participants in the Lenacapavir group remained free from HIV infection, even amidst high levels of sexual exposure, drug use during sex ('chemsex'), and sexually transmitted infections. Poor adherence to daily oral F/TAF or F/TDF observed in these studies may be attributed to various factors, including stigma, dislike or lack of experience with daily pill-taking, and misconceptions about the risk of acquiring HIV infection.

Lenacapvir, a twice-yearly PrEP option, presents an opportunity to address challenges of adherence and persistence, offering substantial protection against HIV infection for diverse populations. According to Gilead Sciences, data from the two trials will be used to support a series of global regulatory filings starting by the end of 2024. The aim is to launch Lenacapavir onto the market in 2025.

Looking ahead: Challenges and hopes

Lenacapavir, the Breakthrough of the Year 2024, brings new and powerful hope in the fight against the HIV epidemic. However, to unleash its full potential for both HIV treatment and prevention, it must be made accessible to everyone in need—a goal that remains out of reach for many. In 2023, the cost of Lenacapavir as an HIV treatment in the United States was $42,250 per patient per year (approximately 650 million Rupiahs!). Gilead Sciences has announced non-exclusive, royalty-free voluntary licensing agreements with six pharmaceutical manufacturers to produce and sell generic Lenacapavir in 120 high-incidence, resource-limited countries. These agreements primarily cover low- and lower-middle-income countries. However, middle-income countries, such as Brazil—where HIV infection rates remain high—are excluded from these agreements. These countries will be forced to pay Gilead’s prices for Lenacapavir unless they successfully challenge unmerited patents on the drug.

UNAIDS has applauded Gilead's announcement but strongly urges the company to extend voluntary licensing agreements to all low- and middle-income countries. They also welcomed Gilead’s statement of commitment to non-profit pricing but emphasized the urgency of specifying an actual affordable price. Research supported by the Make Medicines Affordable Campaign (MMA) estimates that generic Lenacapavir could initially be mass-produced for $63–$93 per patient per year (PPPY), and with production volumes of 10 million, costs could fall further to $26–$40 PPPY. Efforts to oppose unmerited patents are underway, with MMA partners filing patent oppositions in Argentina, India, Indonesia, Thailand, and Vietnam.

Further research on Lenacapavir explores its use in combination with other drugs and the potential for yearly injections, fueling optimism for future

advancements. Hopes are high for the years ahead; however, the core principle of UNAIDS, **'Leave no one behind**,' must remain central to ensure equitable access and to envision a world free of HIV.

May I close this talk with: Happy New Year! Let's move forward together and hope for a year filled with successful breakthroughs!

References

- Bekker, L.G., et al., 2024. Twice-yearly Lenacapavir or daily F/TAF for HIV prevention in cisgender women. New England Journal of Medicine.
- Cohen, J., 2024. The long shot. Science (New York, NY).
- Dvory-Sobol, H., et al., 2022. Lenacapavir: a first-in-class HIV-1 capsid inhibitor. Current Opinion in HIV and AIDS.
- Kelley, C.F., et al., 2024. Twice-yearly Lenacapavir for HIV prevention in men and gender-diverse persons. New England Journal of Medicine.
- Link, J.O., et al., 2020. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature.
- Neverette, N.C., et al., Lenacapavir: Playing the long game in the new era of antiretrovirals. Clinical Pharmacology & Therapeutics.
- Prather, et al., 2023. Lenacapavir: A first-in-class capsid inhibitor for the treatment of highly treatment-resistant HIV. American Journal of Health-System Pharmacy.
- Segal-Maurer, S., et al., 2022. Capsid inhibition with Lenacapavir in multidrug-resistant HIV-1 infection. New England Journal of Medicine.
- Wen, Z., et al., 2024. Treatment as the Best Prevention: Twice-yearly Lenacapavir, a game changer in ending the AIDS epidemic. Viruses.
- https://attheu.utah.edu/health-medicine/anti-hiv-drug-u-biochemist-helped-developed-named-breakthrough-of-the-year/
- https://makemedicinesaffordable.org/hiv-community-based-organizations-are-fighting-patent-monopolies-on-lenacapavir/
- https://www.gilead.com/news/news-details/2024/gilead-signs-royalty-free-voluntary-licensing-agreements-with-six-generic-manufacturers-to-increase-access-to-lenacapavir-for-hiv-prevention-in-high-incidence-resource-limited-countries
- https://www.npr.org/sections/goats-and-soda/2024/12/12/g-s1-37662/breakthrough-hiv-lenacapavir
- https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2024/october/20241002_gilead-lenacapavir

"We're driven by curiosity to discover things that we don't understand. It's not so different from other kinds of adventures. The same thing that drives people to climb mountains drives us to discover how molecular machines work."

- Wesley Sundquist, PhD.

SPORT & LIFESTYLE

STAY ACTIVE DURING THE HOLIDAY SEASON

By: Maria Lestari

The holiday season is a time often associated with indulgence, relaxation, and gatherings. While these aspects contribute to its charm, the period also poses a risk of reduced physical activity, which can have negative health implications. Staying active during the holidays is essential to keep physical health, mental well-being, and overall quality of life.

Physical Health Benefits

Physical activity is fundamental to supporting cardiovascular health, muscle strength, and metabolic efficiency. Research has consistently shown that even short-term inactivity can result in adverse health outcomes. For instance, Booth et al. (2017) found that periods of reduced activity can lead to insulin resistance, loss of muscle mass, and increased fat deposition. During holidays, individuals often experience a caloric surplus due to festive meals, making it even more critical to engage in regular physical activity to mitigate weight gain and metabolic disruptions.

Additionally, holiday activities such as walking, cycling, or engaging in recreational sports can help individuals meet the World Health Organization's (WHO) recommendations of at least 150 minutes of moderate-intensity aerobic activity per week. Such engagement not only prevents weight gain but also reduces the risk of chronic condi-

tions like hypertension and type 2 diabetes (World Health Organization, 2020).

Mental Health Benefits

The holiday season, while joyous, can also be a source of stress due to social obligations, financial pressures, and the general hustle of festivities. Exercise has been well-documented as a potent stress-reliever. A meta-analysis by Rebar et al. (2015) confirmed that physical activity significantly reduces symptoms of anxiety and depression, due to its role in modulating neurochemical responses, including the release of endorphins.

Incorporating even light exercise, such as yoga or stretching, during the holidays can provide mental clarity, improve mood, and promote better sleep quality—factors crucial for enjoying the holiday season fully.

Enhancing Social Bonds

Physical activity during the holidays can also be a means of fostering social connections. Activities such as family walks, group class exercises, or community sports not only promote physical health but also strengthen relationships. A study by Holt-Lunstad et al. (2010) highlighted the profound impact of strong social bonds on longevity and overall well-being, suggesting that combining physical activity with social interaction amplifies its benefits.

Practical Strategies for Staying Active

Maintaining an active lifestyle during the holidays does not need rigorous gym sessions. Simple strategies include:

1. **Active Festivities**: Engage in holiday-themed physical activities, such as indoor ice skating, dancing, throwing balls, or playing outdoor games.
2. **Set Goals**: Use tools like step counters or fitness apps to track daily movement and set achievable goals.
3. **Prioritize Movement**: Incorporate activity into routines, such as taking stairs instead of elevators or parking farther from destinations.
4. **Family Engagement**: Plan family activities that involve movement, like nature walks or visiting holiday spots on foot.

Conclusion

Staying active during the holiday season is more than a measure to counteract indulgence—it is a commitment to one's long-term physical and mental well-being. By integrating physical activity into holiday traditions and recognizing its multifaceted benefits, individuals can enjoy the festivities while safeguarding their health. As the evidence suggests, movement is not just a routine but a pathway to a healthier and happier holiday season.

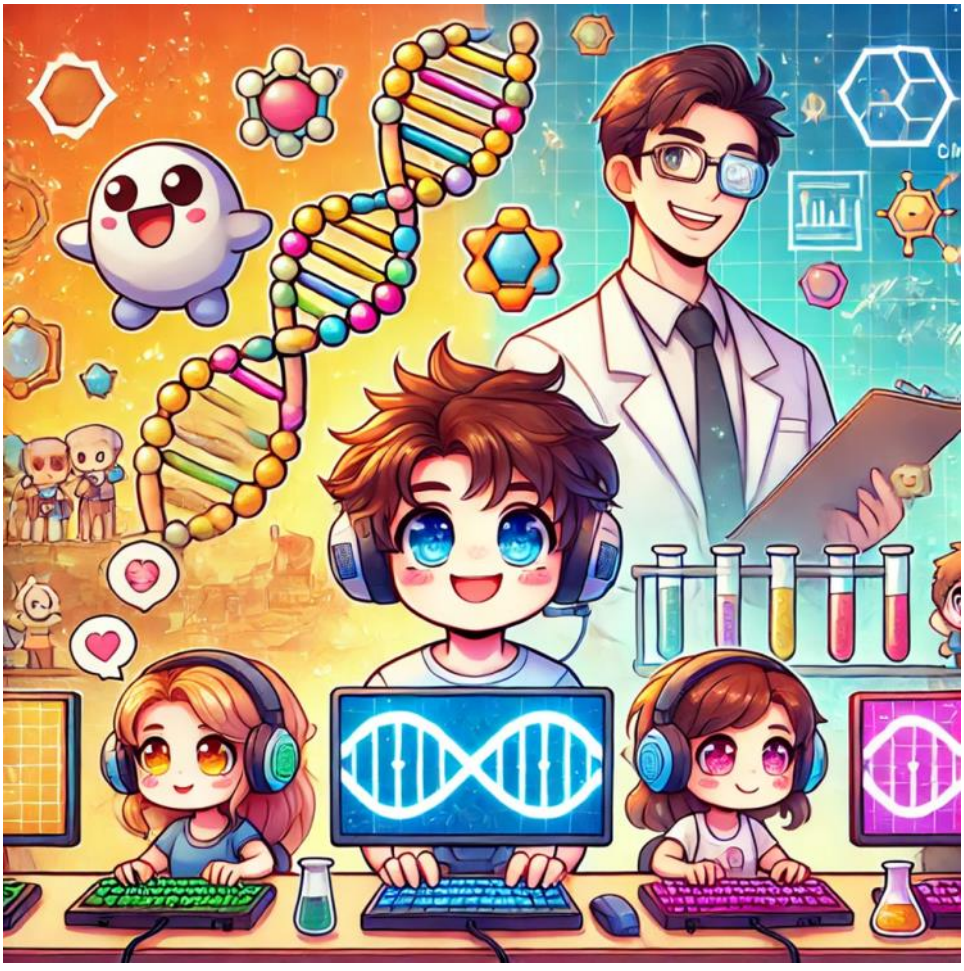
References

- Booth, F. W., Roberts, C. K., & Laye, M. J. (2017). Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology, 2(2), 1143–1211.*
- Rebar, A. L., Stanton, R., Geard, D., Short, C., Duncan, M. J., & Vandelanotte, C. (2015). A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-clinical adult populations. *Health Psychology Review, 9(3), 366–378.*
- World Health Organization. (2020). *Physical activity. Retrieved from https://www.who.int*
- Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine, 7(7), e1000316.*

COMIC CORNER

THE SCIENCE OF PLAY: HOW GAMES UNLOCK NEW DISCOVERIES

By: Aly Diana



Source: DALL-E

I have never considered myself a gamer, but I was thrilled to discover that a mini-game embedded in *Borderlands 3* is reaching its audience—scientists and non-scientists alike—to advance science. This idea struck me as nothing short of brilliant: low cost, high yield, and impactful on a massive scale. During this discovery period, I also learned that this concept has been around for quite some time. It made me reflect and ask myself: Where have I been??? So, I wanted to share what I've found, ensuring that no one else feels left behind.

Below are brief explanations and stories about how games are improving science. The history of using games for scientific discovery can be traced back to 2008 with the introduction of Foldit. Foldit was one of the first citizen science games to engage the public in solving real-world scientific problems. It allowed players to predict the structure of proteins by manipulating 3D models in a game-like interface. Foldit's innovative approach demonstrated that human intuition and pattern recognition could outperform algorithms in certain tasks. The success of Foldit inspired the creation of numerous other citizen science games that have since revolutionized research fields, from genomics to quantum physics. This approach not only acceler-

ates problem-solving but also makes cutting-edge science accessible to the general public.

Another fascinating example is Borderlands Science, a mini-game embedded within the popular video game *Borderlands 3*, introduced in 2020. Borderlands Science presents players with puzzles that involve connecting colored nodes in a grid-like format. Unbeknownst to players, these puzzles represent real-world DNA sequences, specifically the genetic makeup of gut microbiomes. By solving these puzzles, players help scientists align and analyze microbial DNA sequences more efficiently. The game leverages the human brain's pattern-recognition abilities to correct errors in DNA sequence alignments, a task that would otherwise require significant computational resources. The collective effort of millions of players has enabled researchers to process vast amounts of genomic data, advancing studies on microbiomes and their impact on human health. Borderlands Science demonstrates how seemingly simple games can harness collective intelligence to address complex scientific challenges.

Gamification also has the potential to break down silos between disciplines. Researchers developed a game to simulate the spread of misinformation on social media. Players assumed different roles, such as fact-checkers or content creators, and strategized to either amplify or mitigate the spread of false information. The game's design encouraged interdisciplinary collaboration, bringing together behavioral scientists, data analysts, and communications experts to tackle a shared challenge. This collaborative model illustrates how games can serve as neutral platforms for addressing complex, multifaceted problems. By fostering teamwork and shared understanding, games have the potential to generate insights that might otherwise be missed in traditional research settings.

As gaming technology continues to evolve, its applications in research are poised to grow. Virtual and augmented reality, for instance, offer immersive environments for simulating real-world phenomena, from climate change to molecular interactions. Meanwhile, advances in artificial intelligence could enable games to adapt dynamically to player strategies, further enhancing their utility as research tools.

Games are no longer just a pastime—they are powerful engines of innovation. By engaging diverse participants, enabling large-scale data collection, and fostering interdisciplinary collaboration, gamification is reshaping how research is conducted and who can participate. As this trend continues, the boundaries between play and discovery will blur, unlocking new frontiers in science. I hope this brief comic corner can inspire people to tap into their creative side, sparking ideas that are both novel and useful. Perhaps this could even inspire a New Year's resolution!

References

- Dadaczynski K, Tolks D, Wrona KJ, Mc Call T, Fischer F. The untapped potential of Games for Health in times of crises. A critical reflection. Front Public Health. 2023 Feb 28;11:1140665. doi: 10.3389/fpubh.2023.1140665.
- Sarrazin-Gendron, R., Ghasemloo Gheidari, P., Butyaev, A. *et al.* Improving microbial phylogeny with citizen science within a mass-market video game. *Nat Biotechnol* (2024). https://doi.org/10.1038/s41587-024-02175-6.

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