INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

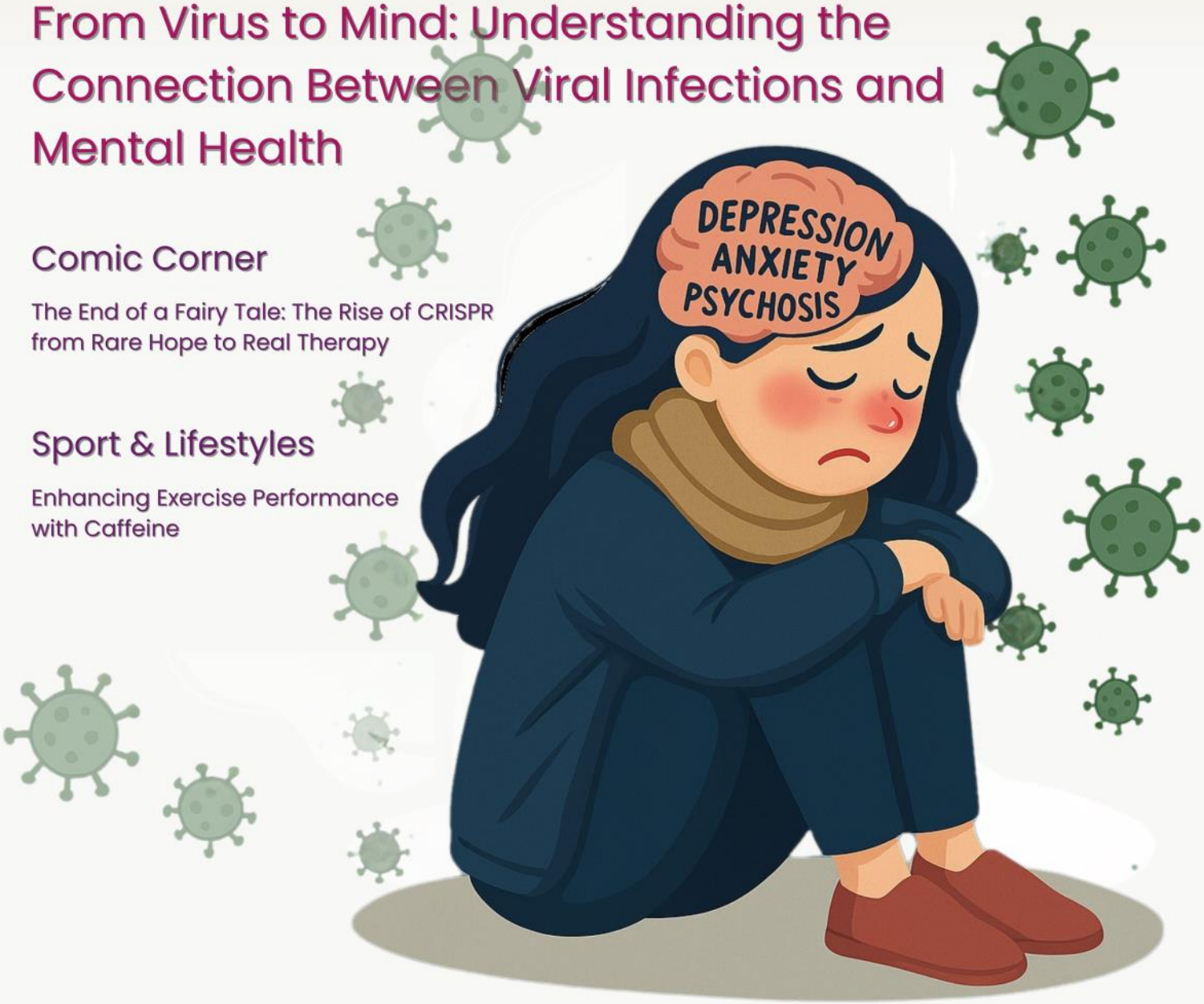
KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

April 2025

Science Corner

From Virus to Mind: Understanding the Connection Between Viral Infections and Mental Health



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HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2025

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newsletter

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FEATURES

STUDY UPDATES

InVITE & PROACTIVE

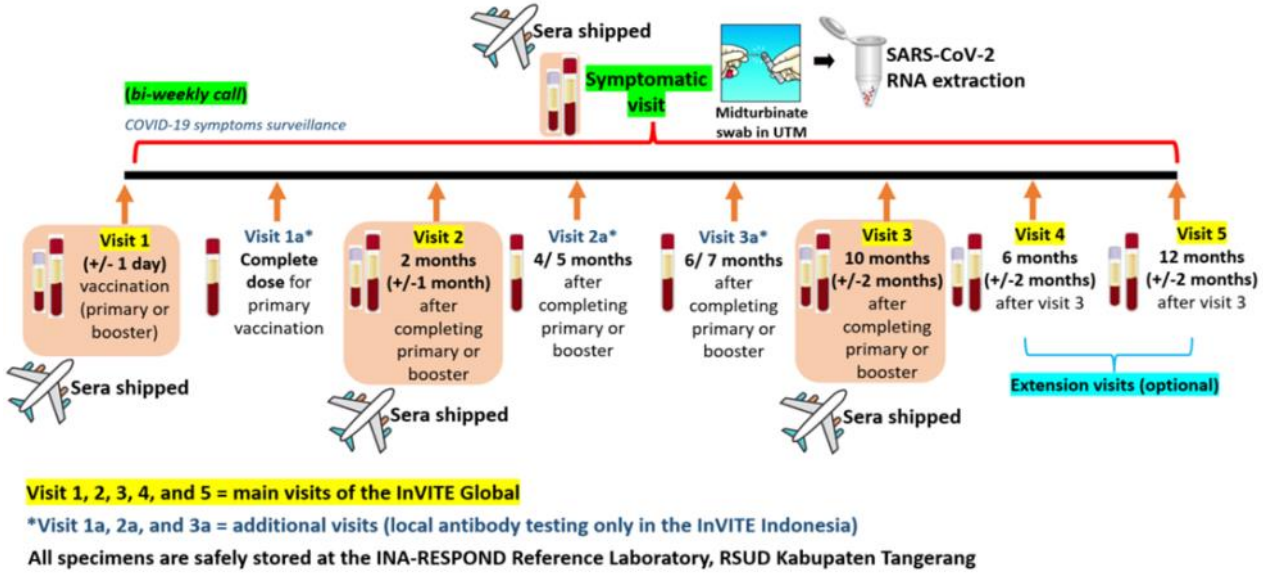
By: Eka Windari R., Nur Latifah Hanum, Restu Amalia Mukti

InVITE

Following the Site Closeout Visit conducted on February 19, 2025, the InVITE study activities involving the study teams and subjects at each study site have been officially completed. Currently, the remaining activity is the preparation of the Final Report, which will include comprehensive information covering the entire activities of the InVITE study—from the beginning to its completion.

The Final Report will contain details on the Background, Study Design, Study Workflow, Ethics Approval History, Monitoring Activities, Study Specimen Accountability, Subject Status, Study Results with corresponding discussions (including information on any publications in international journals based on the study results), Subject Safety Reports, a List of Protocol Deviations, and the Conclusion. The Final Report's completion target is by the end of April 2025. It will be submitted in May 2025 as a supporting document for the study closure notification to the hospital directors at each study site and the RSUD Kabupaten Tangerang Ethics Committee.

In addition, following the successful shipment of participants' sera from Visits 1–3 and Symptomatic Visits, the planned shipment of the remaining InVITE specimens is still in progress. This shipment includes SARS-CoV-2 RNA extracted from midturbinate swab specimens collected in Universal Transfer Media (UTM) from Symptomatic Visits and serum specimens from extension Visits 4 and 5. The Material Transfer Agreement (MTA) for this shipment is handled separately from the previous shipment, as Visits 4–5 and some Symptomatic Visits were still ongoing at the time of the initial MTA process. Additionally, the shipment plan was revised due to regulations concerning potential



Visit 1, 2, 3, 4, and 5 = main visits of the InVITE Global

*Visit 1a, 2a, and 3a = additional visits (local antibody testing only in the InVITE Indonesia)

All specimens are safely stored at the INA-RESPOND Reference Laboratory, RSUD Kabupaten Tangerang

poliovirus in biological specimens—from transporting mid-turbinate swabs in UTM to shipping extracted RNA instead. A new MTA Committee and updated regulations have since been established, including a streamlined review process through the official MTA submission website. However, as the website is currently under maintenance, the required MTA documents—including the draft agreement and appendices—were submitted via email on March 20, 2025. The submission is currently under review by the MTA Committee, and the study team is maintaining active communication with the MTA Secretariat. The team hopes to receive approval soon, as the laboratory testing at the Central Laboratory must be completed by the end of 2025, requiring the shipment to proceed as scheduled in June 2025.

INA-PROACTIVE

As of December 22, 2023, a formal notification was submitted to the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia–Cipto Mangunkusumo Hospital (KEPK FKUI–RSCM), confirming that all subject visits for the INA-PROACTIVE study had been completed across participating sites. **Comprehensive documentation of the study, from initiation to completion, has been compiled in a Final Report, which was submitted via the KEPK FKUI–RSCM website on March 25, 2025, as part of the official study closure process.**

With a robust dataset comprising 4,336 people living with HIV (PLWH) enrolled from 19 hospitals across Indonesia, the INA-PROACTIVE study holds strong potential to generate beneficial insights that can improve HIV care and policy in the country. Several impactful dissemination activities were also highlighted in the Final Report, demonstrating that the study has meaningfully built upon the study team's hard work and the subjects' valuable contributions. Two members of the study team—Neneng Aini (Clinical Research Associate) and Wahyu Nawang Wulan (Laboratory Technologist)—utilized the study data for their academic research at Universitas Indonesia. Neneng successfully earned her Master of Public Health degree with a thesis titled "*Factors Associated with Antiretroviral Therapy Adherence in PLWH in Jakarta*". Nawang also graduated with a doctoral degree in Biomedical Science, defending her dissertation entitled "*Establishing a Method for Identification of Recent HIV Infection and Genotypic Characterization of HIV-1 in Newly Diagnosed Individuals in Indonesia*".

When the INA-PROACTIVE study was still ongoing, preliminary findings were presented at several international conferences. Dona Arlinda (Protocol Principal Investigator) shared a poster titled "*HIV Viral Suppression Rate at Enrolment, Status at One Year, and Associated Factors to Non-Suppression Among Outpatient Adults at 19 Hospitals in Indonesia*" at the International Society for Infectious Diseases (ISID) Congress in Kuala Lumpur, Malaysia (November 17–20, 2022). Aly Diana (Manuscript Writing and Publication Specialist) presented two posters— "*A Prospective Observational Cohort Study of HIV Infection in Indonesia: Baseline Characteristics and One-Year Mortality*" and "*Late Presentation Among PLWH at 19 Referral Hospitals in Indonesia: Trends and Characteristics from the INA-PROACTIVE Cohort*"—at the 72nd American Society of Tropical Medicine & Hygiene (ASTMH) Annual Meeting in Chicago, Illinois (October 18–22, 2023). Additionally, Nawang delivered a recorded presentation titled '*Development of a Multiassay Algorithm (MAA) to Identify Recent HIV Infection in Newly Diagnosed Individuals in Indonesia*' at the 36th Annual Meet-

ing of the Japanese Society for AIDS Research, held in Hamamatsu, Japan (November 18–20, 2022). She also presented '*Transmission Dynamics of HIV-1 CRF01_AE in Indonesia*' at the 31st International Dynamics & Evolution of Human Viruses Meeting in Squamish, Canada (June 20–22, 2024).

Following the completion of study database cleaning and locking, the study team enthusiastically proceeded with data analysis and manuscript development, resulting in publications in high-impact journals. Nawang's analysis of the MAA was refined and published in iScience on October 20, 2023. The main manuscript, which serves as the foundation for future publications, titled "*A Prospective Observational Cohort Study of HIV Infection in Indonesia: Baseline Characteristics and One-Year Mortality*", was published in BMC Infectious Diseases on January 20, 2025. With the Final Report now submitted, data analysis and manuscript preparation using INA-PROACTIVE study data remain ongoing. We hope this largest cohort study of PLWH in Indonesia will enhance and support national HIV care and inspire further research across the country.

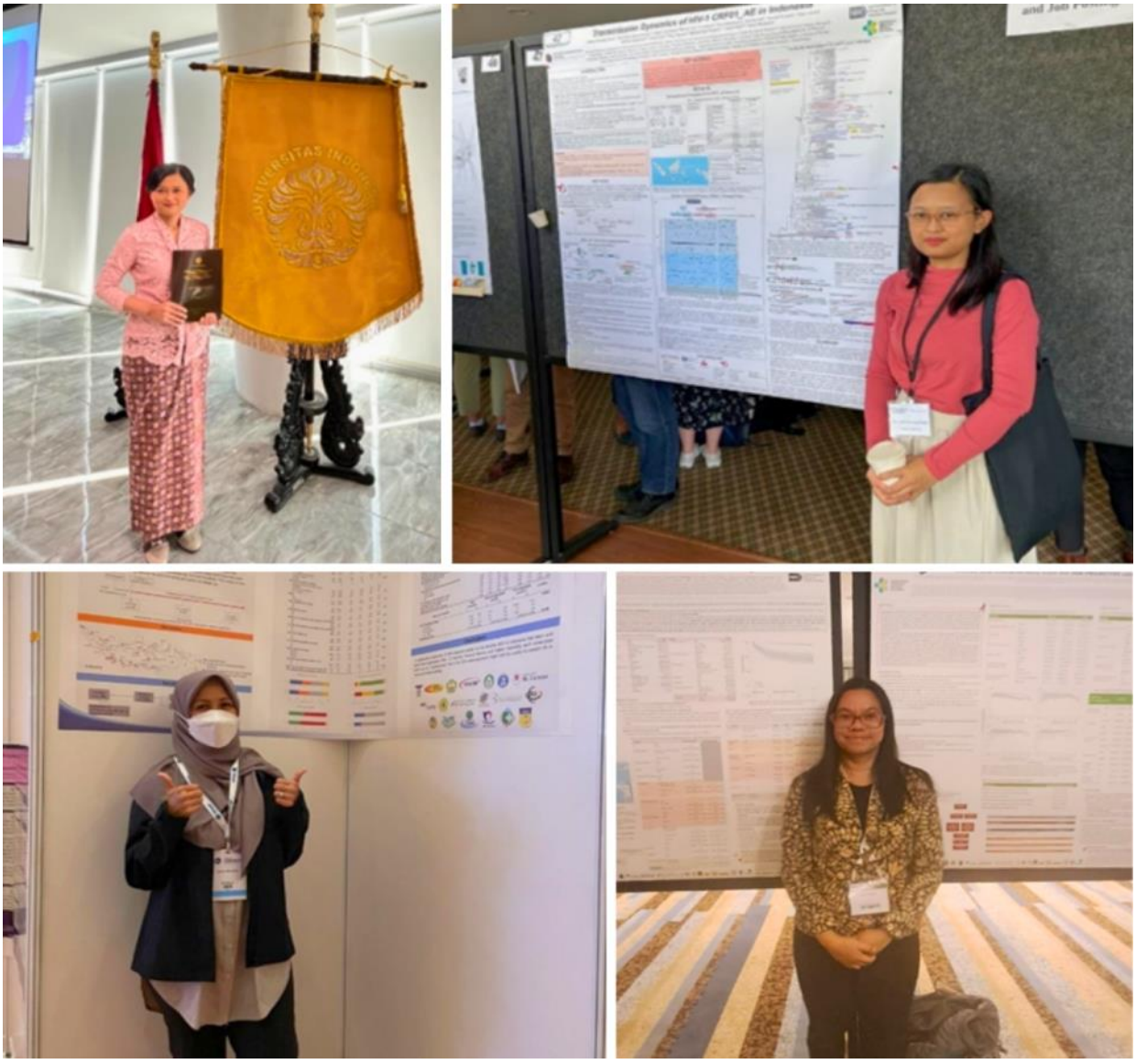


Figure 1. Documentation During Presentation Using INA-PROACTIVE Data

SCIENCE CORNER

FROM VIRUS TO MIND: UNDERSTANDING THE CONNECTION BETWEEN VIRAL INFECTIONS AND MENTAL HEALTH

By: Rifaa'ah Rosyiidah, Adhella Menur

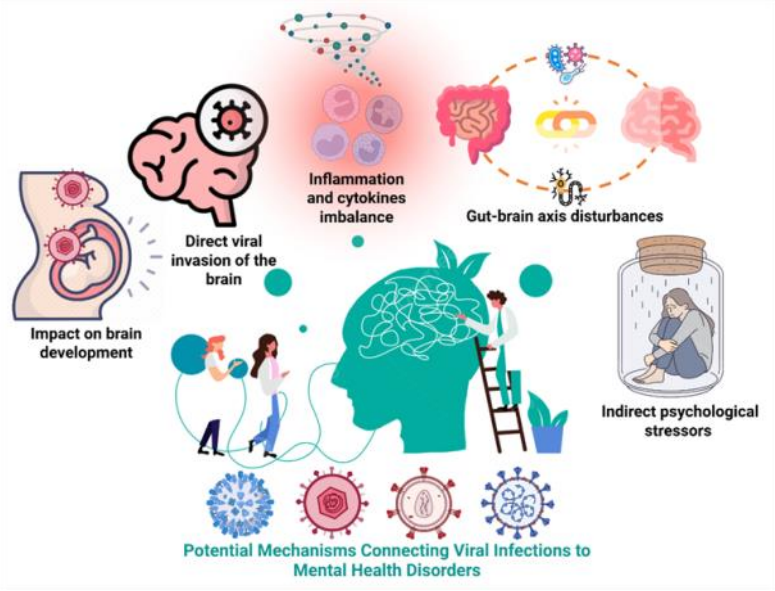
Mental health significantly influences our well-being, productivity, relationships, and overall quality of life. As one of the leading causes of global disability, mental disorders have seen a substantial rise in prevalence, from 654.8 million cases in 1990 to 970.1 million in 2019, as per the 2019 Global Burden of Disease study. Depression and anxiety are major contributors, while disorders like schizophrenia and bipolar disorder, though less common, profoundly affect individuals and families.

Mental disorders arise from genetic, environmental, personality, and biological factors, including changes in specific brain structures. Although it might seem unrelated, researchers are exploring how infectious diseases affect mental health. Viral infections are now believed to play important roles in mental disorders. From general complaints of feeling blue during flu to historic observations, such as the 1918 H1N1 influenza virus pandemic—where a notable increase of about 30% in psychosis and depression was recorded among survivors. Similar patterns emerged during the 2003 severe acute respiratory syndrome (SARS) epidemic, with survivors experiencing higher rates of post-traumatic stress disorder (PTSD) than the general population. During the COVID-19 pandemic, the prevalence of depression increased by about 27.6%, and anxiety increased by about 25.6% in 2020 compared to the previous period. These observations connect the dots from viral infections to our minds.

Research into various viruses, including influenza, herpes simplex virus (HSV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), and SARS-CoV-2, has shed light on their impacts on mental health, particularly in relation to the limbic system—this network of brain regions, which includes the amygdala, hippocampus, and hypothalamus, is crucial for regulating emotions, behavior, motivation, and memory. Understanding these connections can help improve treatments and develop strategies to prevent mental health issues. This edition will discuss theories connecting viral infections to mental disorders, explore specific examples of viral infections related to mental disorders, and suggest future directions.

Mechanisms behind the connection

Viral infections can contribute to mental disorders through several mechanisms. Some viruses directly infect and damage brain cells (neurons), while others trigger immune responses that disrupt brain function. Some viruses can persist in the brain long-term, subtly altering neural networks. Several biological and psychological mechanisms are as follows:



Impact on brain development during pregnancy

Prenatal exposure to certain viral infections has been implicated in altering brain development trajectories. The second trimester of pregnancy is particularly critical as it is a time when the fetal brain undergoes extensive growth and differentiation, making it vulnerable to disruptions. This disruption can be mediated by direct viral effects on the fetal brain if the virus manages to cross the placenta. Additionally, maternal immune activation, characterized by transferring immune products like cytokines from the infected mother to the fetus, can further impact development. These significantly heighten the risk of developing psychiatric conditions such as schizophrenia and autism spectrum disorders (ASD) later in life.

Direct viral invasion of the brain

Viruses can reach the brain through hematogenous spread, entering the bloodstream to cross the blood-brain barrier, or neural spread (e.g., HSV, CMV, Zika virus, and Borna disease virus-1), which travels along peripheral nerves to the brain. These invasions can damage neurons or crucial brain-supporting cells known as glial cells, including astrocytes, oligodendrocytes, and microglia. Damage to these cells can disrupt neurotransmitter systems and neuroplasticity (the brain's ability to adapt and reorganize itself), leading to behavioral abnormalities and neuroinflammation associated with neuropsychiatric symptoms. For example, Figure 1 illustrates how certain viral infections affect glial cells, contributing to depression.

Viral infections can have profound effects on the brain's glial cells, disrupting their essential functions and contributing to depression. Astrocytes, essential for regulating neurotransmitters and maintaining neural balance, can be impaired by viruses, leading to disrupted signaling and increased neuroinflammation that exacerbates depressive symptoms. Oligodendrocytes, which form the myelin sheath, may also be damaged, impairing signal transmission and causing structural brain changes associated with depression. Addi-

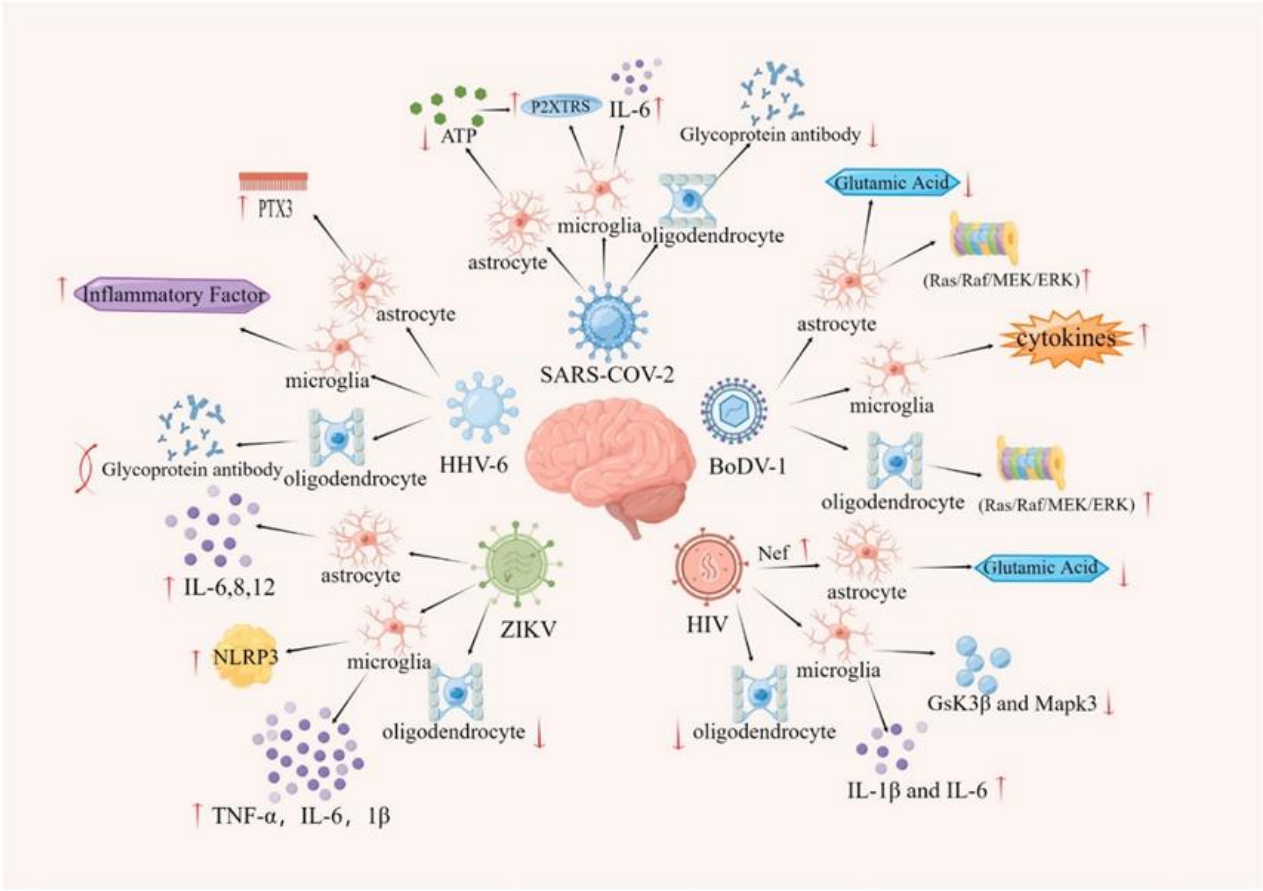


Figure 1. Impact of viral infections on depression via glial cell mechanisms.

tionally, viral infections can activate microglia to a pro-inflammatory state, releasing cytokines like IL-6 and TNF-α that further drive neuroinflammation. This prolonged activation disrupts synaptic function and contributes to neurodegeneration, deepening the link between viral infections and depressive disorders. These mechanisms highlight the complex interplay between viral infections and neurobiological changes that predispose individuals to depression.

Indirect impact via inflammation and cytokine imbalance

Inflammation is now widely recognized as a potential contributor to mental disorders such as depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. During viral infections, the release of pro-inflammatory cytokines like IL-6, IL-1β, TNF-α, and IFN-γ—either produced within the brain or entering from the bloodstream—can impair critical brain functions such as neuroplasticity, synaptic function, and neurogenesis. Moreover, an immunopathologic event such as a cytokine storm during systemic inflammation can compromise the blood-brain barrier, intensify neuroinflammation, and result in long-term psychiatric consequences.

Researchers are also wondering why many individuals who survive sepsis—a severe response to infection—often develop mental disorders such as anxiety and PTSD. A study using animal models has pinpointed that during a specific time in sepsis, specific neurons in the central amygdala, called PKCδ+ neurons, become overly active. These neurons link to areas of the brain involved in emotion regulation, enhancing fear and anxiety circuits, which may predispose survivors to long-term mental health issues. In this study, researchers discovered that silencing these neurons during the acute phase of sepsis could prevent the development of anxiety and fear-related behaviors later on. They achieved this through two methods: genetic manipulation to turn off the neurons temporarily and administering levetiracetam (LEV), an anti-seizure medication already approved for human use.

	IL-1α	IL-1β	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12	IL-17	IL-18	TNF-α	IFN-γ	TGF-β	CRP	sTNF-R1	sTNF-R2	IL-1RA	sIL-6R	sIL-2R	CCL2	CCL11	CXCL10
MDD		NC	NC	NC	NC	↑	NC	NC	↑		↑	↑			↑			↑		↑			
BD		NC	NC	↑	NC	↑/NC	NC	↑				↑	NC			↑	NC	↑/NC	↑	↑		↑	↑
SCZ		↑	NC			↑	↑	↑	↑			↑	↑					↑	↑				
PTSD		↑/NC		NC		↑		↑/NC				↑	↑		NC								
ASD	NC	↑		NC		↑	↑			NC		↑	↑								↑	↑	
INFL		↑		↑↑		↑	↑	↑↑	↑↑		↑	↑	↑								↑↑		↑
HSV		↑				↑	↑	↑/NC	↑/NC			↑	↑										↑
CMV		↑				↑	↑	↑				↑	↑/NC										↑
HIV		↑	↓	↑		↑	↑	↑				↑	↓								↑		
SARS-CoV-2		↑	↑	↑↑		↑	↑	↑↑	↑	↑	↑↑	↑	↓	↑	↑						↑		↑

Table 1. Cytokine profiles in mental disorders and viral infections (Lorkiewicz, P., & Waszkiewicz, N. 2024. https://doi.org/10.3389/fcimb.2024.1423739).

This table compares the cytokine profiles of individual mental disorders with the cytokine profiles of viral infections to facilitate the comparison of similarities or differences between them. The cytokine profile of viral infections was constructed using the same method as that of the mental disorders.

ASD = autism spectrum disorder; BD = bipolar disorder; CMV = cytomegalovirus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; INFL = influenza; MDD = major depressive disorder; NC = not changed; PTSD = post-traumatic stress disorder; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SCZ = schizophrenia; ↑ = increase; ↓ = decrease; ↑↑ = increase only in severe infections.

Gut-brain axis and microbiome disturbances

The term "gut feeling" is more than just a saying—it reflects the real connection between our gut and mental health. This link is governed by the gut-brain axis, a complex communication system that involves our gut microbiome, which significantly influences our emotions and psychological well-being. Disruptions in the gut microbiome can alter the production of essential neurotransmitters like serotonin, which is vital for regulating our mental health. Such imbalances can result in anxiety and depression. Moreover, changes in the gut microbiota can affect the vagus nerve—the direct communication pathway between the gut and the brain—impacting brain functions and potentially exacerbating neuropsychiatric symptoms.

Indirect psychological stressors

Indirect psychological stressors associated with viral infections—such as fear, stigma, and social isolation—play a significant role in exacerbating mental health issues. While not directly biological, these stressors can influence the balance of the hypothalamic-pituitary-adrenal (HPA) axis—the body's system for regulating stress hormones. This dysregulation can lead to an excessive or uncontrolled release of cortisol, adversely affecting brain function. Chronically high cortisol levels are linked to structural and functional changes in critical brain areas like the hippocampus and prefrontal cortex, which are essential for regulating emotions and memory. A study has identified disorders of the HPA axis as a primary factor in the pathophysiology of depression.

Viruses and associated mental disorders

Influenza Virus

The connection between influenza virus infection during pregnancy and the subsequent risk of schizophrenia in offspring is one of the earliest explored connections between viral infections and mental disorders. Some epidemiological studies indicate that individuals whose mothers contracted influenza during the second trimester are at an increased risk of developing schizophrenia. This association is likely due to maternal immune activation, as the virus rarely crosses the placenta. Additionally, maternal antibodies generated in response to the virus may engage in molecular mimicry, mistakenly targeting and disrupting fetal brain proteins due to their structural similarities. These disruptions in fetal brain development can potentially lead to changes that increase the risk of schizophrenia in adulthood. Additionally, maternal influenza virus infection is associated with up to a fivefold increase in the risk of offspring developing bipolar disorder with psychotic features but not bipolar disorder without psychotic features. A study also indicated that individuals with mood disorders are more likely to have antibodies against influenza A or B viruses, with influenza B linked to a more than 2.5-fold higher risk of suicide attempts and psychotic symptoms. Further research is needed to explore these associations.

Herpes Simplex Virus and Cytomegalovirus

Both HSV and CMV are associated with several mental disorders through complex mechanisms. These include impacts from maternal infections affecting fetal brain development and from latent infections that can reactivate, causing persistent low-grade inflammation and impacting mental health. Research suggests that maternal infections with HSV and CMV may elevate the risk of schizophrenia in offspring. Additionally, elevated anti-HSV-2 IgG antibodies in maternal plasma during mid-pregnancy have been associated with a higher risk of ASD in male offspring. Exposure to HSV-2 has been shown to double the risk of depression. CMV's influence on depression is more nuanced; higher anti-CMV antibody titers seem to increase depression risk, indicating that the intensity of the immune response might influence depressive symptoms. Furthermore, HSV is associated with cognitive disorders and may contribute to the development of late-onset Alzheimer's disease.

Human Immunodeficiency Virus

HIV significantly impacts mental health, leading to conditions like cognitive decline and depression, classified under HIV-associated neurocognitive

disorders (HAND). These arise from both the direct invasion of the brain by HIV and the virus's indirect effects, such as chronic inflammation and neurodegeneration. HIV is closely associated with a high incidence of depression, primarily due to its activation of chronic immune responses that increase pro-inflammatory cytokines and reduce levels of the brain-derived neurotrophic factor (BDNF), which is crucial for neuronal health and plasticity. The virus also directly affects glial cells, such as astrocytes and oligodendrocytes, disrupting neural communication and exacerbating neuroinflammation, which in turn worsens depressive symptoms. Beyond depression, HIV patients are also more susceptible to psychosis, which can manifest primarily without any neurological disorders or secondarily due to opportunistic brain infections or metabolic dysfunctions. Moreover, the stigma and psychological stress associated with HIV amplify these mental health challenges, leading to isolation and heightened anxiety and depression. People living with HIV (PLWH) are also at a significantly increased risk of suicide, with a meta-analysis reporting a global suicide mortality rate for PLWH at 10.2‰, which is 100 times higher than the general population at 0.09‰.

SARS-CoV-2

SARS-CoV-2, the virus responsible for COVID-19, has been associated with mental disorders, with many individuals recovering from the infection reporting increased instances of anxiety, depression, and cognitive impairments. These issues are often associated with persistent neuroinflammation and hypoxic brain injury. SARS-CoV-2 can cause mitochondrial damage that disrupts energy metabolism, contributing to depressive symptoms. It also impacts nutritional status by reducing levels of tryptophan, essential for serotonin synthesis, thereby affecting mood regulation. Additionally, elevated levels of IL-6, a cytokine critical in the immune response to COVID-19, have been connected to schizophrenia and other psychotic disorders, with some preliminary studies indicating higher levels of coronavirus antibodies in people with these mental health conditions. Moreover, the long-term effects of the virus, known as post-acute sequelae of SARS-CoV-2 infection (PASC) or "long COVID," often manifest as chronic fatigue syndrome and brain fog, highlighting the enduring mental health implications of SARS-CoV-2. A 2022 study by Taquet et al. demonstrated that the delta variant poses a higher risk of various mental disorders compared to the alpha and omicron variants, as shown in Table 2.

Type of disorder	Variant α	Variant δ	Variant o
Anxiety disorder	HR 0.99	HR 1.10	HR 1.04
Mood disorder	HR 1.04	HR 0.99	HR 1.20
Cognitive impairment	HR 0.93	HR 1.13	HR 0.94
Psychotic disorder	HR 0.94	HR 1.15	HR 0.96
Insomnia	HR 0.94	HR 1.19	HR 0.95

Table 2. Comparison of the hazard ratio of specific mental disorders depending on the variant of the SARS-CoV-2.

Future Directions

Understanding the connection between viral infections and mental health is complex because many factors are involved. We're left with many questions: How do different viruses, each with their own unique effects, contribute to mental health? Can we pinpoint a specific virus as the cause of a particular mental disorder? And why do only some people who get infected develop mental disorders? With ongoing advancements in neuropsychiatry and neurovirology, the possibilities for unlocking those answers are limitless.

Several key steps are essential to enhance our understanding of the connection between viral infections and mental health. Firstly, **interdisciplinary research** is crucial; collaboration among virologists, neurologists, psychiatrists, and immunologists is necessary to decipher the complex pathways. Future research should aim to elucidate the molecular and genetic bases of virus-induced neuroinflammation to identify potential therapeutic targets. Secondly, **early detection and preventive measures** are vital. Developing biomarkers to predict mental health outcomes in patients with viral infection could enable early intervention. Screening for cytokine imbalances or neuroinflammation markers in high-risk groups may facilitate timely and effective management of potential mental disorders. Thirdly, **holistic treatment approaches** should be integrated into viral infection treatments, addressing biological and psychological factors to enhance patient outcomes and quality of life. Pharmacological advances, such as therapies targeting neuroinflammation or specific viral pathways, promise to alleviate the mental health burdens associated with these infections. Lastly, **public health policies** need improvement. Public education about the potential mental health impacts of viral infections can help reduce stigma and promote timely mental health support. Integrating mental health considerations into pandemic preparedness plans, including vaccination strategies, is crucial for mitigating the mental health consequences of future crises. **Let's commit to preventing viral infections from impacting our bodies and minds!**

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SPORT & LIFESTYLE

ENHANCING EXERCISE PERFORMANCE WITH CAFFEINE

By: Risky Dwi Rahayu

Caffeine is one of the most widely used stimulants in the world. People usually consume it in coffee, tea, soft drinks, or chocolate, but it is also added to many sports-nutrition products such as gels, chewing gum, energy shots, and energy drinks. Research shows that, when used correctly, caffeine can improve exercise performance (its so-called ergogenic effect).

Caffeine was first placed on the International Olympic Committee (IOC) list of banned substances in 1984 and on the World Anti-Doping Agency (WADA) list in 2000. At that time a positive test meant a urine caffeine concentration above 15 µg mL; this limit was reduced to 12 µg mL in 1985. In 2004 caffeine was removed from the banned list, but WADA still monitors its use. Athletes are advised to keep urine caffeine below the same threshold, which is roughly equal to consuming 10 mg kg body mass over several hours—about three times the amount usually needed to enhance performance.

How Caffeine Works

Caffeine's performance-boosting effects involve several body systems. In the central nervous system it blocks adenosine receptors, reducing feelings of tiredness and increasing alertness. This blockade also raises dopamine and norepinephrine levels, which sharpen concentration and motivation while lowering the perception of effort and pain during exercise. In skeletal muscle caffeine helps release more calcium from the sarcoplasmic reticulum, which can increase the force of each

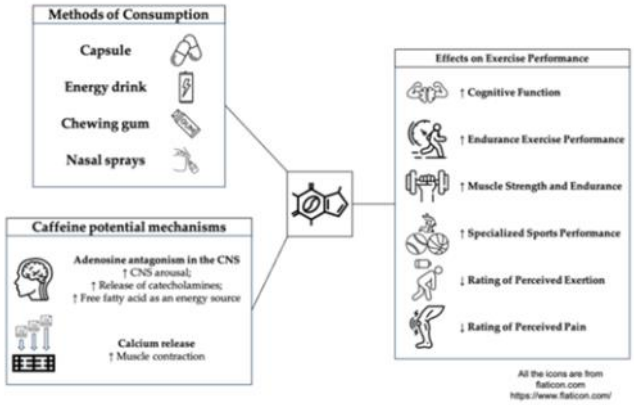

Figure 1. Mechanism of caffeine action. ↑ increased, ↓ decreased.

contraction. Finally, in fat tissue it promotes lipolysis, raising blood free-fatty-acid levels and sparing muscle glycogen.

Peak blood caffeine appears 30–90 minutes after ingestion, and the average half-life is about five hours. The liver enzyme CYP1A2 breaks down most of the caffeine, while 1–3 % leaves the body unchanged in urine. Regular caffeine users may develop tachyphylaxis—a short-term reduction in some effects such as heart-rate or blood-pressure rise—but studies show that the performance benefits remain similar in both habitual and non-habitual users.

Most evidence supports moderate doses of 3–6 mg kg^{-1} taken 30–60 minutes before activity. At these levels athletes typically report lower perceived exertion and fatigue, longer time to exhaustion, and better power output in time-trial events.

Research on strength, power, and muscular endurance is less consistent, but small benefits often

appear with the same 3–6 mg kg^{-1} dose taken 30–90 minutes before training or competition. Even a one-to-three-percent increase in maximal force can matter for athletes in power-oriented sports such as powerlifting or weightlifting. Caffeine may also improve single-sprint and intermittent-sprint efforts, although results for repeated-sprint performance remain mixed and need further study.

Individual Differences

Not everyone responds the same way to caffeine. Genetics—especially variations in the CYP1A2 and ADORA2A genes—training status, and habitual intake all play a role. People with the AA version of CYP1A2 ("fast metabolizers") usually clear caffeine quickly, whereas those with AC or CC ("slow metabolizers") may experience stronger cardiovascular effects and, in the general population, a higher risk of hypertension or heart problems with heavy coffee consumption.

Practical Guidelines

For most endurance events, the greatest benefits come from consuming 3–6 mg of caffeine per kilogram of body mass about 30–60 minutes before the start. The same dosage works for strength and power sports, while sprint or high-intensity interval training shows more variable results but generally follows the same timing and amount.

Caffeine can be delivered in several ways. Traditional coffee or tablets remain the most common methods used in studies. Chewing gum provides faster absorption through the lining of the mouth; a dose of 200–300 mg taken immediately before or even during prolonged exercise can be particularly helpful for well-trained athletes. Mouth rinsing with a caffeinated solution for 5–20 seconds may stimulate brain receptors and improve performance without swallowing the caffeine. Nasal sprays or inhaled powders enter the bloodstream quickly through nasal tissue, but the research base is still small. Gels, bars, and energy drinks are popular among endurance athletes, although the effects of energy drinks also come from other ingredients such as taurine.

Combining caffeine with other supplements requires care. The current evidence suggests that caffeine and creatine should be taken at separate times because a simultaneous dose does not add extra benefit and may reduce creatine effectiveness. In contrast, adding caffeine to a carbohydrate drink or gel is more ergogenic than carbohydrate alone.

Typical side-effects include insomnia, jitteriness, a faster heartbeat, and stomach upset. Athletes should start with low doses—around 1–2 mg kg^{-1}—during training to test tolerance before using caffeine in competition.

Conclusion

Caffeine can be a useful aid for endurance, strength, and many high-intensity activities when taken in the right amount and at the right time. Because responses vary, athletes should experiment during training, not on race day, to find their personal "sweet spot."

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COMIC CORNER

THE END OF A FAIRY TALE: THE RISE OF CRISPR FROM RARE HOPE TO REAL THERAPY

By: Aly Diana

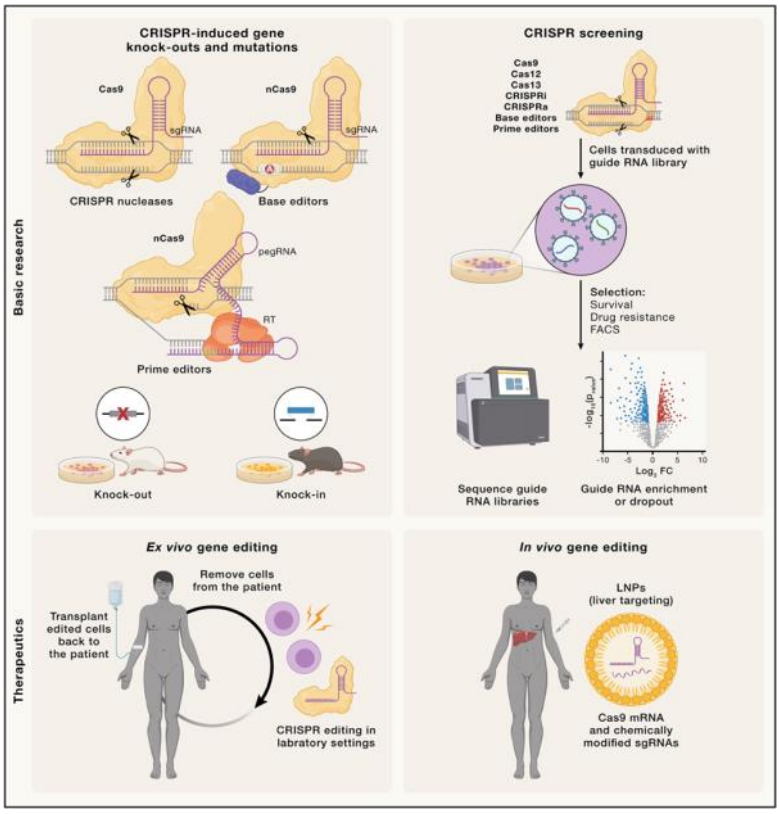

Figure 1. Applications of CRISPR genome editors relevant to human health (https://www.cell.com/cell/fulltext/S0092-8674(24)00111-9)

A while ago, I discussed CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)—and honestly, the idea of editing genes still fascinates me. I remain deeply hopeful about what it could mean for the future of medicine. From time to time, I check on its progress, and I was delighted (even if a little late!) to learn that a CRISPR/Cas9-based therapy—exagamglogene autotemcel, or exa-cel—was approved in the United Kingdom in November 2023 and by the U.S. Food and Drug Administration in December 2023. It was cleared as a treatment for sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT). This milestone feels like a powerful leap forward: it proves that CRISPR is no longer a fairy tale—it is here, and it works. It also renews hope for patients facing other genetic and even infectious diseases.

Exa-cel has already shown impressive efficacy in clinical trials. In a Phase 3 study of patients with severe SCD, 97 percent (29 of 30) were free from severe vaso-occlusive crises for at least 12 consecutive months after treatment. Among individuals with TDT, 91 percent (32 of 35) achieved transfusion independence following exa-cel therapy. The safety profile of exa-cel was generally favorable, and no deaths or cancers occurred. After treatment, participants are invited to enroll in a 13-year follow-up study (CLIMB-131) to monitor the durability and safety of this gene-editing approach over time.

CRISPR technologies are evolving rapidly. The discovery of Cas9 sparked a wave of research that uncovered other RNA-guided enzymes suitable for genome editing. Among these, Cas12a stands out for its distinct target-recognition pattern and generally higher precision. Scientists have since identi-

fied a range of smaller, more specialized nucleases—such as Cas12g and Cas13—that offer advantages in delivery and RNA editing. These newer enzymes also enable applications such as mRNA editing and diagnostic tools. Although each enzyme has its own strengths and limitations—such as target restrictions or potential immunogenicity—the expanding toolkit allows greater flexibility and precision in gene editing.

CRISPR has revolutionized biomedical research by enabling precise disease modeling, large-scale genetic screening, and even biological recording systems. In diagnostics, it is used for fast, sensitive detection of pathogens. In therapy, gene editing has progressed from preclinical models to clinical trials, employing both in vivo and ex vivo approaches. Ex vivo editing has advanced particularly far in cancer treatment through genetically modified immune cells. A recent review in Cells (2024) is highly recommended for a deeper understanding—it is an engaging read.

In infectious-disease research, one especially interesting focus is HIV. CRISPR has been studied against HIV for more than a decade. The first demonstration of CRISPR/Cas9 technology applied to HIV-1/AIDS treatment appeared in 2013, when researchers suppressed HIV-1 gene expression in Jurkat cell lines by targeting two critical regions within the HIV-1 long terminal repeat: the NF-κB binding motifs in the U3 region and the TAR sequences within the R region. Many studies have followed. One of the most recent and promising experiments involved HIV-1 ADA-infected $CD34^+$ NSG-humanized mice. Treatment with long-acting ester prodrugs of cabotegravir, lamivudine, and abacavir, combined with native rilpivirine, was followed by dual CRISPR/Cas9 gene editing that targeted CCR5 and HIV-1 proviral DNA. This sequential approach achieved viral suppression, restored absolute human $CD4^+$ T-cell counts, and eliminated replication-competent virus in 58 percent of the infected mice. Dual CRISPR therapy facilitated the excision of integrated proviral DNA in infected human cells within live animals. These findings highlight the diverse potential targets within the HIV-1 genome that could be exploited to reverse latency in infected cells. However, further research is essential to identify the most effective genomic targets and to optimize the therapeutic use of CRISPR/Cas9 technology in HIV-1 treatment.

Although using CRISPR to defeat HIV will require more time, the approval of exa-cel shows what is possible. Personally, it is hard not to feel hopeful. Seeing CRISPR move from theory to therapy feels like living in an era of real scientific magic. And although CRISPR-based treatments for infectious diseases such as HIV are not here yet, they are closer than ever.

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