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Review Article

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The Role of Host Genetics Regulating Proteins in HIV-1 Susceptibility: Epidemiological and Demographic Insights on HIV-1 in Indonesia (2022)

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Abstract

Human Immunodeficiency Virus type 1 (HIV-1) remains a global public health concern, marking 52,995 cases in Indonesia alone, dominated with CRF01_AE strain which is classified as an X4 strain or a virus that uses CXCR4 co-receptor. This highlights the urgent needs to develop therapies that utilize CXCR4 inhibitors to modulate HIV-1 infection and replication. The aims of this study were to assess the epidemiological and demographic insights on HIV-1 in Indonesia in 2022, and connecting it to the dominated strain to further assess various host genetics known to promote HIV-1 infection, focusing on the co-receptors CCR5 and CXCR4. A systematic review was conducted, analyzing published studies and the 2022 HIV/AIDS report from the Ministry of Public Health of Indonesia. Additionally, the study evaluated the therapeutic potential of CXCR4 antagonists, including AMD3100, AMD070, BPRCX807, and MCo-CVX-5c, known for their anti-HIV-1 activity. Among the listed antagonists, AMD070 and MCo-CVX–5c are advancing among the others, leading to a potential most advanced combination antiretroviral therapy (cART). This research contributed to the development of personalized treatment strategies for HIV-1 by providing insights into the genetic factors influencing co-receptor regulation and HIV-1 susceptibility.

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INTRODUCTION

HIV-1 is a complex virus capable of infecting and replicating in a variety of cell types, including CD4+ T cells, macrophages, and dendritic cells.[1] This virus has been a global focus due to its complexity and impact on public health. In Indonesia, the trend of HIV-1 cases has fluctuated significantly over the years. The population of people living with HIV (PHIV) rose from thousands to tens of thousands, reaching a peak in 2019 with 50,282 individuals diagnosed across the country. [1]

Efforts to prevent and treat HIV-1 in Indonesia by the Ministry of Health Republic of Indonesia have been quite thorough to the point they were able to suppress the rate of HIV-1 in previous years; these efforts include awareness campaigns, treatment programs, and prevention strategies. However, the fluctuating trend suggests that additional challenges persist, such as inadequate distribution about HIV-1 prevention and inconsistent access to healthcare. The continued presence and spread of HIV-1 highlight the need further research in creating more strategies of prevention and treatment to address these gaps effectively.[2]

The study of host genetics has revealed that host genetics can influence HIV-1 by affecting viral entry, replication, immune response, and disease progression. To illustrate, genetic variants in the CCR5 gene, which encodes the co-receptor used by HIV-1 to enter cells have been shown to influence HIV-1 susceptibility. [3] Individuals with a homozygous deletion of CCR5Δ32 are resistant to HIV-1 infection, whereas those with a heterozygous deletion have a lower risk of infection and a slower disease progression. Other genetic variants in the CCR5 gene and other viral entry genes, such as CXCR4 and CD4, have also been linked to HIV-1 susceptibility. [3]

Interestingly, while CCR5 is predominantly used in the early stages of HIV infection, the virus's shift to CXCR4 usage is often associated with accelerated disease progression.[4] Understanding and targeting CXCR4 offers a promising avenue to intervene in this critical stage of HIV progression. In addition to that, the exploration of CXCR4 antagonists provides insights into a broader spectrum of HIV-1 strains. CXCR4-tropic viruses, although less common in early-stage infections, play a significant role in the later stages and in cases of treatment failure.

The objective of this study is to explore the role of CXCR4 antagonists and their impact on HIV-1 pathogenesis, this research aims to identify novel therapeutic strategies and contribute to the broader understanding of HIV-1 infection dynamics. The outcomes of this study could provide valuable insights for designing more effective prevention and treatment strategies, particularly in regions like Indonesia, where HIV-1 remains a significant public health challenge.

MATERIALS AND METHODS

Materials

The systematic review was conducted on PubMed and Google Scholar ranging from 2013-2023 as well as the 2022 quarterly and annual report on HIV AIDS by the Ministry of Health Republic of Indonesia. Additionally, BioRender was utilized to create schematic illustrations of host genetics and other molecules, indicated by figures without citation.

Methods

Eligibility Criteria

This study was a systematic review using data from studies that have been

published from 2013-2023 regarding host genetics regulating proteins that are susceptible to HIV-1. The exclusion criteria were the following: used language other than Indonesia or English, could not be accessed, did not show data of interest, did not specify X5 or X4 strain, did not identify year or location, CXCR4 antagonists without anti-HIV activity, and host genetics other than regulating proteins and are promoting HIV-1 resistance.

Literature Review Process

Literature search was done on PubMed and Google Scholar with keywords: "Human Immunodeficiency Virus type 1 OR HIV-1 OR CCR5 OR CXCR4 OR X5 strain OR X4 strain OR Antiretroviral Therapy OR ARV OR Host Genetics Regulating Proteins OR CXCR4 Antagonists". The search was set to obtain studies from 2013-2023.

Study Inclusion and Data Extraction

A total of 45 research articles were collected based on search results from each database and were imported into Zotero to remove duplicates. Next, title, abstract, and results were screened based according to predefined inclusion and exclusion criteria. The data from studies included that were extracted are: first author, publication year, study area, and specimen tested. Research articles lacking sufficient details and results were excluded, leaving a final selection of 35 articles.

The main outcomes in this review, focusing on the trends and distribution of HIV-1 in Indonesia in 2022, were presented in bar graphs and percentages, categorized by region. In addition, the potential CXCR4 antagonists were thoroughly compared based on their efficacy and therapeutic potential.

RESULTS AND DISCUSSION

Rate of HIV-1 in Indonesia (2022)

According to the Annual HIV AIDS report by The Ministry of Health Republic of Indonesia in 2022 as shown on Figure 1, the first quarter of 2022 (January—March) had 10,525 cases diagnosed. It then increased to 11,000 in the second quarter (April—June), the third quarter (July—September) continued the upward trend with 12,588 cases. There was a more substantial rise in the fourth quarter (October—December), where the number of diagnosed cases reached 18,782.

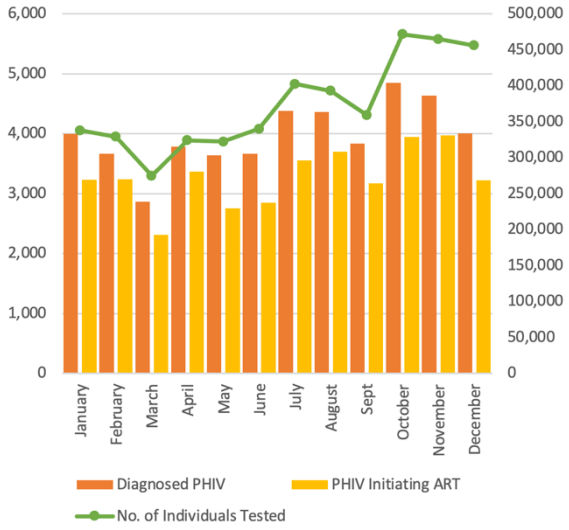

Figure 1. HIV-1 in Indonesia year 2022[5]

The data reveal a consistent increase in the number of HIV diagnoses throughout the year, with the highest number recorded in the last quarter. The increasing trend could reflect various factors, such as increased testing and reporting, spread of HIV or increase rate of HIV infection, or heightened awareness and diagnostic activities. However, the data may not be representing accurately as there are nine districts/cities which have not submitted any HIV data to the Ministry of Health Republic of Indonesia to the last quarter or December 2022, as attached in Table 1.

Table 1. List of districts/cities which have not submitted their HIV data as per December 2022[5]

Province	District/City
East Nusa Tenggara	Alor, Central Sumba
North Sulawesi	Siau Tagulandang Biaro Islands
Southeast Sulawesi	North Konawe
North Maluku	Tailabu Island
West Papua	Maybrat, Pegunungan Arfak
Papua	Nduga

The case distribution, as shown in Figure 2 displays the number contributed by each province for the diagnosed people with HIV (PHIV) and the PHIV initiating ART in Indonesia in 2022. However, it can be identified that the top 3 provinces contributing to the diagnosed PHIV (West Java, East Java, and Central java) are different, in terms of order, or province with the top 3 provinces contributing to PHIV initiating ART as shown in Figure 3 (West Java, East Java, and Central Java).

The different order can be attributed to several factors, including the access to healthcare, awareness and education, stigma and discrimination, and economic factors. The access to healthcare can be one of the causes for the factors where some regions may have better healthcare infrastructure and access to medical services, awareness, and education where regions with higher awareness or better public health campaigns about HIV can lead to more people getting tested and starting treatment. Stigma and discrimination which leads regions with higher stigma may lead to fewer people initiating ART despite being diagnosed, and, lastly, economic factors where wealthier regions may have a higher percentage of diagnosed individuals and starting ART due to better financial access to healthcare services.

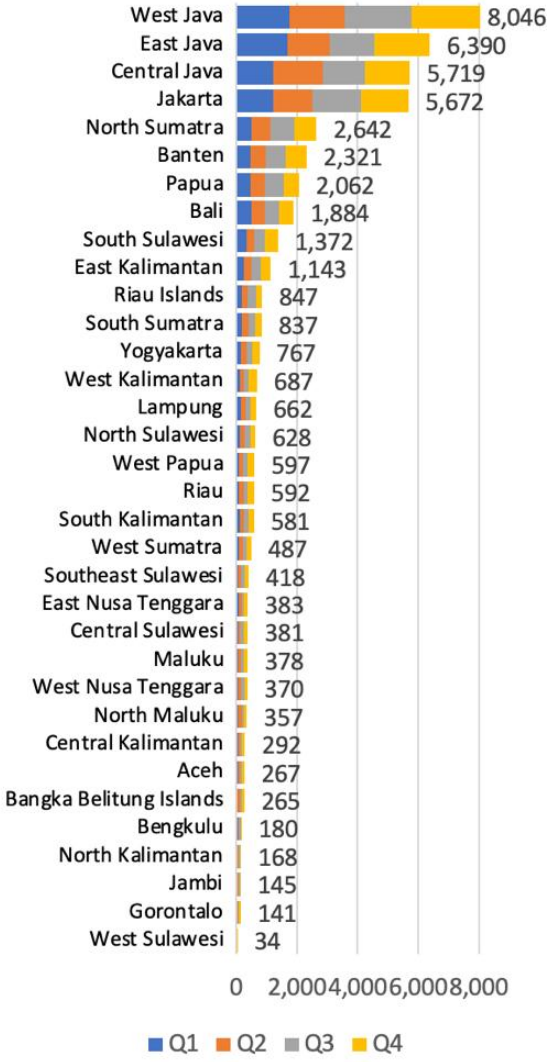

Figure 2. Diagnosed people with HIV in Indonesia year 2022[5]

According to Figure 4 on the age distribution for PHIV in 2022, the majority is within the range of 25-49 years old for 66.6%, followed by 20-24 years old for 17.7%, over 50 years old for 9.3%, 15-19 years old for 3.9%, and both below 4% to the range of 4-15 years old for 1.2% each. Regarding gender, the PHIV is dominated by male for 71% and female 29%.

The potential reasons for the age distribution can be affected by several factors, including sexual activity, awareness and education, and mother-to-child transmission. The dominant age falls within the 25-49 years old which is typically the most sexually active age range, hence leading to a higher risk of HIV transmission due to a higher rate of

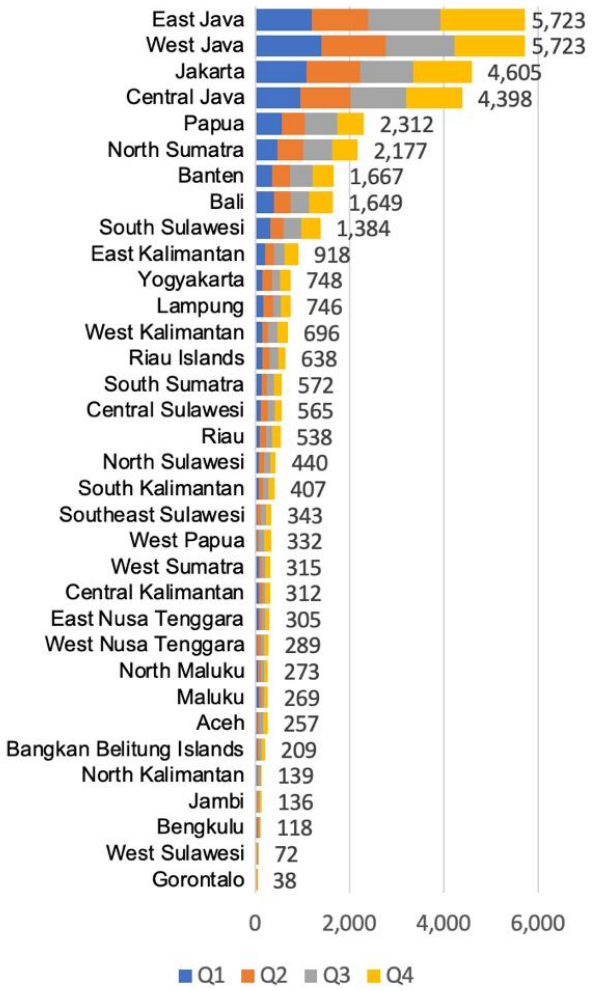

Figure 3. People with HIV initiating ART in Indonesia year 2022[5]

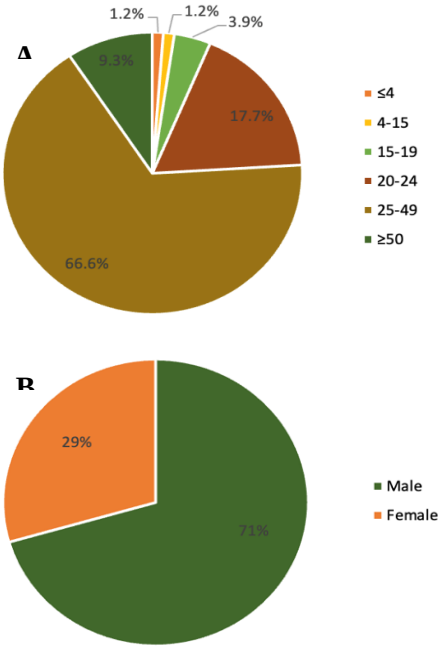

Figure 4. (A) Age distribution and, (B) gender distribution of people with HIV year 2022[5]

change of partner and potentially unprotected sexual encounters. Whereas younger age groups may have access to education about HIV prevention, lowering the rate of HIV. Lastly, mother-to-child transmission, which is the reason as to how a very young age group can also be infected with HIV.

As for the gender distribution factors, the higher percentage of males could be due to riskier behaviors that are more prevalent among men, such as unprotected sex with multiple partners, hiring sex workers, or engaging in sex with other men, which is a significant risk factor for HIV. Biological factors also play a role in this as women are biologically more susceptible to acquire HIV during heterosexual intercourse than men, and lastly is occupational exposure where men are most likely to work in industries with higher mobility where they may engage with commercial sex workers.

Regarding the population of PHIV, as shown in Figure 5 this is dominated with MSM or men who have sex with men counting for 27.8%, followed by others/unknown for 27.3%, pregnant women for 15.8%, TB (Tuberculosis) patients 12.4%, transgenders 6%, clients of sex workers 4.3%, sex workers 3.1%, high risk couples 1.1%, correctional institution residents 1%, and the least is drug users at 0.5%. TB patients are involved as the bacteria (Mycobacterium tuberculosis) can increase the viral load in people living with HIV, which may increase the infectiousness and eventually accelerate to AIDS.[6] Drug users are also involved as they are most likely being involved in the activity of sharing needles, increasing the HIV rate from the blood transmission.

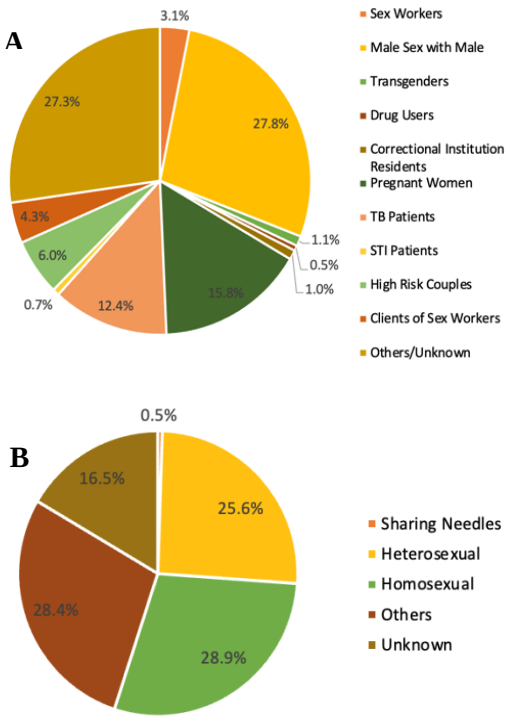

Figure 5. (A) Population and, (B) risk factors of people with HIV in Indonesia year 2022[5]

As for the risk factor, the majority was caused by homosexual intercourse for 28.9%, followed by others (such as blood transfusion, mother-to-child transmission, or traditional practices involving exposure to blood) comprising 28.4%, heterosexual for 25.6%, unknown factor for 16.5%, and sharing needles for 0.5%.

According to Figure 6, the testing number increased up to 761,496 in the last quarter, which could be due to enhanced public health campaigns, improved access to prenatal care, or increased adherence to testing protocols which often recommend HIV screening for all pregnant women. The number of pregnant positive HIV fluctuates from the first to the last quarter which can also be caused by the number of HIV tests. The gap between the number of pregnant women diagnosed with HIV and those receiving ART could be due to the access to treatment, such as limited availability of medication or distance to healthcare facilities, and stigma where they can fear for receiving discrimination. In addition to that, lack of awareness may also be the factor as in the lack of knowledge about the importance of ART for their health and their babies.

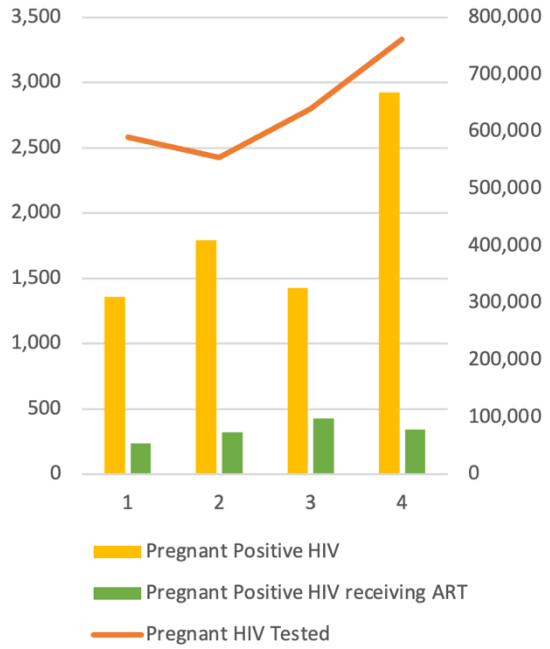

Figure 6. Population of pregnant positive HIV in Indonesia 2022[5]

Table 2. Coverage of HIV diagnosis and ART initiation[5]

Year	Diagnosed PHIV	ART Initiated PHIV
2019	50,282	38,998
2020	41,987	32,925
2021	36,902	30,160
2022	52,992	42,610

PHIV : People with HIV
ART : Antiretroviral Therapy

Table 2 displays data over a four-year period from 2019 to 2022 concerning the number of HIV diagnoses and the initiation of antiretroviral therapy (ART) in Indonesia. In 2019, there were 50,282 HIV diagnoses with 77.6% of those diagnosed starting ART. The following year, 2020, showed a decrease in diagnoses to 41,987 but an increase in the percentage of individuals starting ART to 78.4%.

In 2021, the number of diagnoses decreased further to 32,925, yet the percentage of people beginning ART rose significantly to 81.7%. In contrast, 2022 increased in HIV diagnoses to 52,995, while the percentage of patients initiating ART decreased slightly to 80.4%. The graph highlights a trend where, despite the fluctuations in the number of diagnoses, a consistently high and increasing proportion of diagnosed individuals are starting treatment each year, except for a small decline in 2022.

Regarding the molecular epidemiology of HIV-1 in Indonesia, a recent study investigated HIV-1 subtyping and the identification of HIV Drug Resistance (HIVDR) in 105 individuals infected with HIV-1 who lived in different cities between 2018 and 2019. The results, shown in Table 3 revealed that CRF01_AE is the predominant HIV-1 strain causing the epidemic, accounting for 81.9% of infection cases. Subtype B follows with a prevalence of 12.4%, while CRF02_AG, CRF52_01B, and a recombinant strain between CRF01_AE and CRF02_AG account for 3.8%, 1%, and 1.0% of cases, respectively.[7] This is corroborated by a study carried out in 2022 and 2023, which indicates the prevalence of CRF01_AE in Medan and Makassar.[8,9]

Table 3. HIV-1 subtype prevalence in Indonesian cities in 2018-2019[7]

Subtype	Infection Case
CRF01_AE	81.9%
Subtype B	12.4%
CRF02_AG	3.8%
CRF52_01B	1%
CRF01_AE / CRF03_AG	1.0%

Subtype AE is known to be a part of X4 tropic virus, which is supported by research conducted in 2019 regarding co-receptor tropism and genetic characteristics. Among the 16 X4-tropic viruses studied, 12 of them are CRF01_AE, two CRF55_01B, one subtype B and one URF. The determination that CRF01_AE is a part of X4-tropic viruses was made through the analysis of co-receptor usage in different genotypes of HIV-1.[10] In the study, the genotypes of the viruses were determined by analyzing the pol genes of the subjects. Hence, the increased rate of HIV-1 and the majority of AE subtype led to a higher urgency to conduct more research in enhancing the available treatment or to create new avenue within the treatment strategies, specifying to ones that are targeting CXCR4.

Role of Host Genetics Regulating Proteins in HIV-1 Susceptibility

The complication of the host genetics study lies within their variations, analogous to how CCR5 highly contributes to HIV-1 susceptibility but CCR5-Δ32 is well known to be resistant to HIV-1; other host genetics also have their own kinds and lead to different results.[15]

Among the host genetics studied for this research, five host genetics are widely known to promote HIV-1 susceptibility, including cyclophilin A (CypA), certain alleles of apolipoprotein E (APOE) and Human Leukocyte Antigen (HLA), CCR5, and CXCR4 with the summarized elaboration displayed in Table 4.

Cyclophilin A

Cyclophilin A (CypA) plays a significant role in promoting HIV-1 susceptibility through its interaction with the HIV-1 capsid protein. This interaction is crucial for the virus's ability to infect human primary cells, such as peripheral blood mononuclear cells (PBMCs) and CD4+ T cells. The mechanism by which CypA enhances HIV-1 infections involves several

Table 4. Summarized host genetics regulating proteins in HIV-1 susceptibility

No	Host Genetic	Role in promoting HIV Susceptibility	Mechanism of Action	References
1	Cyclophilin A (CypA)	The virus' uncoating process	Prevents TRIM5α from binding to the viral capsid and promote delayed uncoating leading to a successful viral integration	Selyutina et al.[10]
2	Apolipoprotein E (ApoE)	Viral entry and LTR transactivation	ApoE4 helps easier viral entry and is less effective in restricting Tat-mediated long terminal repeat (LTR) transactivation--a viral protein necessary for HIV-1 thus allowing more Tat protein to be converted into LTR for HIV formation	Chen et al.[13]
3	Human Leukocyte Antigen (HLA)	HIV suppressive and non-suppressive immune response	The non-suppressive immune response or non-protective HLA B allele (HLA-B*35) producing monofunctional CTL with limited recognition for infected cells	Lunardi et al.[14]
4	CCR5/CXCR4	Viral entry	The chemokine receptor for HIV viral entry	Chen et al.[13] Lunardi et al.[14]

key steps, including CypA-Capsid interaction, protection from TRIM5α restriction, influence on reverse transcription, and differential effects in cell types.[10]

The contact between CypA and the HIV-1 capsid is crucial for the successful infection of human primary cells, as CypA binds to the capsid.

Research has demonstrated that administering Cyclosporin A (CsA), a substance that hinders the binding of CypA to the HIV-1 capsid, effectively suppresses HIV-1 infection in both PBMCs and CD4+ T cells.[13] The next key step is its protection against TRIM5α restriction, CypA binding to the HIV-1 core is thought to protect the virus from the restriction factor human tripartite motif 5 alpha (TRIM5α), which is known to inhibit HIV-1 infection by recognizing and binding to the viral capsid, leading to its premature disassembly and degradation. By binding to the capsid, CypA prevents TRIM5α from exerting its restrictive effects as a host genetic promoting HIV-1 resistance.[10]

Moreover, studies have shown that when the interaction between CypA and capsid protein is disrupted in CD4+ T cells, it greatly reduces the efficiency of reverse transcription, which is a critical step in the HIV-1 life cycle. This implies that CypA helps the virus's early stages of replication in addition to shielding it from restriction factors. Finally, compared to Jurkat cells (a human T cell line), the effect of CypA on HIV-1 infection appears to be more pronounced in primary human lymphocytes. This suggests that CypA's role in promoting HIV-1 susceptibility may be especially significant in the context of primary human cells.[11]

Figure 7 displays a comparative view of the presence of Cyclophilin A (A) and the absence of Cyclophilin A (B), where, in the presence of CypA, it blocks the TRIM5α in binding to the HIV, leading to delayed uncoating and a successful integration, promoting HIV disease progression. Whereas in the absence of CypA, TRIM5α would take place in binding to the capsid of HIV, being

recognized by the innate immune response and causing the virus to undergo premature uncoating and the failure of integration, preventing the HIV disease progression.[12]

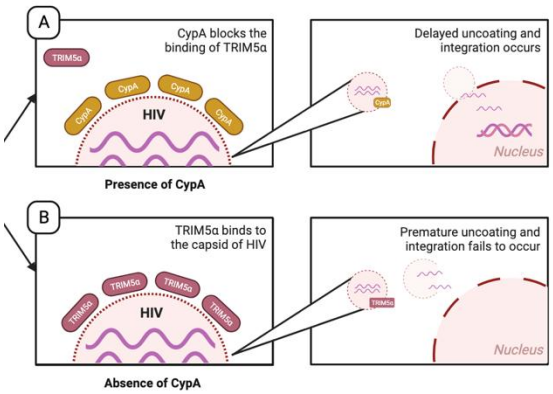

Figure 7. Cyclophilin A mechanism of action in promoting HIV disease progression

Apolipoprotien E (APOE)

Apolipoprotein E (APOE) is a protein that is responsible for regulating the breakdown and use of fats in the body. However, it also has a notable impact on the health and diseases of the nervous system. In the case of HIV-1, APOE has been found to influence the progression of the disease and the development of HIV-associated neurocognitive disorders (HAND). APOE exists in three main forms, known as isoforms - APOE2, APOE3, and APOE4. These isoforms differ from each other by a single amino acid substitution, specifically an interchange between arginine and cysteine at two positions.[13], as shown in Figure 8. These isoforms have been studied for their potential impact on HIV-1 pathogenesis.

APOE has a well-established role in neurological disorders, particularly Alzheimer's disease and viral diseases. In the context of HIV, the presence of the APOE4 allele has been correlated with an increased risk of developing neurocognitive impairments. APOE4 may exacerbate neuronal damage caused by HIV-1, leading to a more rapid decline in cognitive function.[13]

The differential impact of APOE isoforms on HIV-1 pathogenesis is a subject of ongoing research. APOE2, for instance, is thought to have a protective effect against HIV-related neurocognitive disorders, potentially due to its anti-inflammatory properties. Understanding these variations is crucial for developing targeted interventions to mitigate the neurocognitive impacts of HIV-1 and for tailoring antiretroviral therapy based on individual genetic profiles.[13]

Figure 8 depicts the comparison of ApoE3 and ApoE4 in HIV infectivity, where (A) shows the virus with ApoE4 which interacts with its receptor (HSPG and LDLR) accelerate the contact between HIV and cell membrane which facilitates virus cell entry, whereas the ApoE3 depicted in (B) has a lesser ability in bringing the virus inside the target cell. Figure (C) illustrates that ApoE4 has reduced efficacy compared to ApoE3 (D) in inhibiting Tat-induced long terminal repeat (LTR) transactivation, a crucial viral protein essential for HIV-1 replication, therefore promoting more Tat protein to enter the nucleus for producing LTR required for the virus' formation.

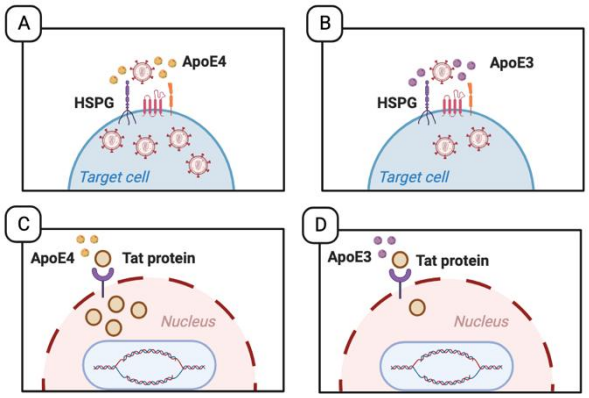

Figure 8. Comparison of ApoE3 and ApoE4 mechanism in accelerating HIV infection

Human Leukocyte Antigen (HLA)

Human Leukocyte Antigen (HLA) molecules are essential for the immune system's capacity to identify and react to infections, such as HIV-1. The HLA system exhibits a high degree of polymorphism, resulting in a wide range of distinct HLA alleles throughout the human population. Each allele has the ability to deliver a unique collection of peptides to T cells. The diversity is essential for the immune system's capacity to effectively counteract a broad spectrum of infections.[14]

HLA Class I molecules, which include HLA-A, HLA-B, and HLA-C, present endogenous peptides, including those derived from viral proteins, on the surface of infected cells. Cytotoxic T lymphocytes (CTLs) recognize these peptide-HLA complexes and can kill the infected cells, thereby controlling the infection. The variability in HLA molecules, particularly in the peptide-binding groove, affects the repertoire of viral epitopes that can be presented. HLA is widely known to promote HIV resistance. However, specific HLA alleles have been linked to greater susceptibility to HIV infection and accelerated disease advancement.[14]

One approach involves the presentation of viral peptides that have a reduced ability to stimulate a robust immune response. HLA-B*35-Px has been linked to rapid HIV-1 disease advancement, as an example. This genotype exhibits a more restricted spectrum of HIV peptides to the immune system, potentially constraining the efficacy of the immunological response. [14]

Another method occurs through the selection of viral escape mutants. The immunological pressure exerted by cytotoxic T lymphocytes (CTLs) might result in the emergence of viral variations that possess alterations in the epitopes they exhibit. This enables the variants to avoid detection by the immune system.16 HLA alleles like HLA-B27 and HLA-B57 are linked to a slower course of disease because the escape mutants they choose usually have a negative impact on the virus's ability to survive and reproduce, resulting in reduced fitness.

However, other HLA alleles may select escape mutants that do not impair viral fitness, thus promoting viral persistence and disease progression. [13] Furthermore, certain HLA alleles may influence the immune response in ways that promote HIV replication. For example, HLA-B*35-Px has been associated with increased inhibitory immunoregulatory impulses, which could potentially enhance HIV replication.[14]

Figure 9 displays the schematic representation of the protective and non-protective HLA B alleles in HIV infectivity, where Figure (A) shows the protective HLA B alleles producing polyfunctional CTL which recognizes more diverse infected cells whereas Figure (B) shows the non-protective HLA B alleles producing monofunctional CTL and its limited ability to recognize diverse types of infected cells.

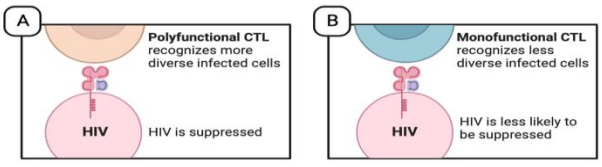

Figure 9. Illustration of the protective and non-protective HLA B allele

CCR5

Next is CCR5 (C-C Chemokine Receptor type 5) which is the necessary receptor for HIV-1 to enter certain immune cells. The HIV-1 virion's surface glycoproteins known as the viral envelope use the chemokine receptor family's CCR5

or CXCR4 co-receptors in addition to the primary receptor CD4 to enter target host cells. Env encodes the envelope glycoproteins, which bind non-covalently to the transmembrane gp31 subunit and surface gp120 subunits of the virion to form trimmers at the lipid membrane.[15]

During the initial stage of viral entry, the gp120 attaches to one or more CD4 primary receptors, causing structural modifications in gp41 and revealing a previously hidden binding site for chemokine receptors. The V3 loop residues of gp120 engage in interactions with the N terminus, which in turn interacts with the bridging sheet of gp120. Additionally, these V3 loop residues interact with residues present in the chemokine receptor binding pocket, as well as in ECL1 and ECL2 of the co-receptor, either CCR5 or CXCR4.[15]

Gp41 and gp120 approach the target membrane through sequential binding to CD4 and a co-receptor. This causes the gp41 domains to go through a complex folding process that results in the formation of a fusion intermediate involving a six-helix bundle. As a result, the target cell membrane's lipid bilayer can be penetrated by gp41's extremely hydrophobic fusion peptide, causing the two membranes to fuse and create a pore that lets the viral capsid enter the infected cells' cytoplasm.[15]

Pre-integration latency can occur when HIV-1 attacks inactive and inexperienced T cells, thereby obstructing the integration of HIV-1 into the genetic material of the host by reverse transcription and then progressing to active or memory cells. In either case, memory cells have the ability to be reactivated, or naïve cells can be stimulated, resulting in the production of infected effector and memory cells.

This process helps to preserve the transcription and translation of HIV-1. Thus, cells that express CCR5 make up the largest portion of HIV-1 latency and serve as a hidden storage of the virus. These can occur due to the infection of quiescent memory T cells, active memory T cells that remain in a memory T cell state, activated thymocytes undergoing transition to naïve T cells, or activated T cells that return to a quiescent memory T cell state.[15]

The identification of the CCR5-Δ32 mutation has offered additional understanding regarding the involvement of CCR5 in determining vulnerability to HIV-1. The mutation leads to the formation of a shortened receptor that is absent from the cell surface, as depicted in Figure 10. Consequently, persons who have two copies of this mutation are immune to HIV-1 infection, whereas those who have one copy experience a slower pace of disease progression.[16]

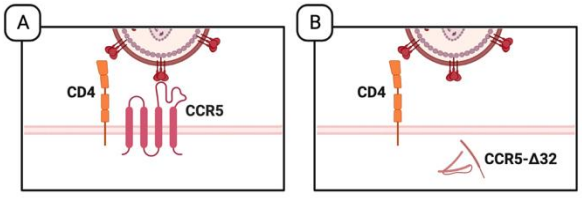

Figure 10. The illustrated comparison between CCR5 and CCR532

The discovery has sparked significant interest in developing therapeutic strategies that explicitly focus on CCR5, either by inhibiting its interaction with gp120 or by mimicking the effects of the Δ32 mutation. The CCR5-Δ32 mutation provides a unique perspective on the relationship between host genetics and susceptibility to HIV-1. This mutation is caused by a 32 base pair deletion in the CCR5 gene, leads to the truncation of the receptor and its inability to be generated on the cell surface.[17]

CXCR4

As previously mentioned, not only CCR5 but CXCR4 (C-X-C chemokine receptor type 4) is also the co-receptor for

HIV-1 entry as shown on Table 5. The different strains of HIV-1 lead to different chemokine receptor utilization. As shown in Table 3, R5 tropic uses CCR5, and X4 tropic uses CXCR4 as their co-receptor. The primary targets of HIV-1 early infection are monocyte-derived macrophages and memory CD4 cells, which are mostly infected by exclusively R5 strains. In contrast, exclusively X4 strains predominate at a later stage and favor naïve and resting T cells.

Table 5. Phenotypic classification of HIV-1 based on co-receptor use[18]

Chemokine Receptor	Natural Ligands	HIV-1
CCR5	CCL3, CCL4, CCL5	R5
CXCR4	CXCL12	X4
CCR5, CXCR4		R5X4
CCR2, CCR3, CCR5		R2R3R5

The primary cause of early infections is R5 tropic viruses, which have a greater attraction to CD4 and a higher level of CCR5 surface expression compared to CXCR4 on CD4+ memory T cells and immature dendritic cells. This influences how effectively the virus can enter the cells. Previous investigations have shown that the transmission of HIV-1 by R5 strains is more effective than X4 strains, as is the multiplication of the virus.[19]

The chemokine receptor CXCR4 plays a crucial role in the vulnerability and advancement of HIV-1 infection. HIV-1 exploits this receptor, in addition to CCR5, to enter CD4+ T cells (CD4TL). The interaction between HIV-1 and CXCR4 plays a vital role in regulating the virulence of the virus, especially in relation to its capacity to induce AIDS.

Research has indicated that viruses that utilize CXCR4 (X4-tropic viruses) tend to exhibit higher levels of pathogenicity compared to those that utilize CCR5. The strains that use CXCR4 are associated with a quicker decline of CD4TL cells and a faster development of AIDS. It is worth mentioning that there is a significant range in the severity of CXCR4-using viruses, suggesting a complicated interaction between viral and host variables in the advancement of the disease.[20]

Therefore, the emergence of CXCR4-tropic HIV-1 viruses represents a significant turning point in the infection's progression. The ability of these viruses to infect a broader range of cells, and the resultant immune system damage they cause are central to understanding the accelerated progression toward AIDS. This knowledge not only aids in prognostication but also underscores the need for targeted therapeutic strategies to combat CXCR4-tropic HIV-1 strains.

Discovery of CXCR4 Antagonists

The clinical implications of the CXCR4 usage by HIV-1 have led to the development of CXCR4 antagonists as potential therapeutic agents. These drugs aim to block the interaction between the virus and CXCR4, thus preventing the virus from entering cells. However, their effectiveness is limited to cases where the virus predominantly uses CXCR4 for entry.[21]

Understanding the role of CXCR4 in HIV-1 infection and its implications for disease progression is crucial for developing targeted therapies and managing late-stage HIV-1 infection.

As research continues, further insights into the molecular mechanisms governing the CCR5-to-CXCR4 switch and the role of CXCR4 in HIV pathogenesis are expected to emerge, offering potential new strategies for intervention.

Table 6. Comparison of CXCR4 antagonists

No	Antagonist	Class	Anti-HIV (IC_{50})	Toxicity (CC_{50})	Pharmaco-kinetics	Development Status	Disease Treatment	References
1	AMD3100 (Plerixafor)	Small molecule	3 nM	>500 µM	Subcutaneous	Terminated in clinical trial for HIV	Stem cell mobilization	Wang et al.[24] Huang et al.[25]
2	AMD070 (Mavorixafor)	Small molecule	10 nM	>100 µM	Oral	Phase 2	HIV	Huang et al.[25]
3	BPRCX807	Small molecule	40.4 ± 8.0 nM	NS	Subcutaneous	Investigational primarily for anticancer effects	Mainly for cancer	Dogra et al.[34]
4	MCo-CVX-5c	Peptide	2 nM	>100 µM	Subcutaneous	Preclinical	HIV	Chaudhuri et al.[32]

NS: Not Specified

CXCR4 is not only known in HIV-1 but also several diseases such as carcinoma and hepatitis, however, up to this day, there has not been a single CXCR4 antagonist that is approved by the FDA for the HIV-1 treatment.[21] The list of CXCR4 antagonists is as listed in Table 6 which compares the class, type, mechanism of action, anti-HIV (IC_{50}), toxicity (CC_{50}), pharmacokinetics, and their potential effectiveness as HIV treatment. There are over 30 CXCR4 antagonists at the present time, including Tachyplesin 1, T22, MSX-11, miR-146, and many more.[22] However, many still lack data and information required for comparison and some are reportedly to have inability to treat HIV-1, hence four CXCR4 antagonists were chosen (AMD3100 (Plerixafor), AMD070 (Mavorixafor), BPRCX807, and MCo-CVX-5c) for a more in-depth analysis rather than a broad overview with limited information, as shown in Table 4.

AMD3100

AMD3100 (Plerixafor) is a small non-peptide chemical that inhibits the CXCR4 receptor. The nitrogen atom that has gained a proton on the ring interacts with the carboxylic acid group on CXCR4, which restricts the binding of CXCL12 to CXCR4. This interaction prevents downstream signaling and controls several physiological activities.[23]

AMD3100 functions as a selective inhibitor of CXCR4 by disrupting its interaction with CXCR4, as depicted in Figure 11. It attaches to CXCR4 and hinders the attachment of CXCL12, thereby impeding the transmission of signals and movement of cells toward the chemical gradient.

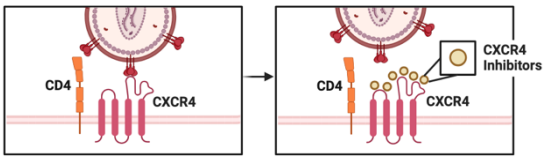

Figure 11. Illustration of CXCR4 Inhibitors

AMD3100 has demonstrated limited efficacy as a partial agonist against the normal form of CXCR4 and can enhance the function of a mutant form of CXCR4 that is constantly active, but only at high dosages.[23] In addition to its investigation for HIV-1, AMD3100 was also studied for its potential in treating WHIM syndrome (a rare immunodeficiency disorder characterized by panleukopenia), brain tumors, and

autoimmune diseases. Furthermore, it has been demonstrated to possess the capacity to synergize with other anti-cancer treatments for conditions such as cervical cancer, pancreatic illnesses, mesothelioma, ovarian cancer, hepatocellular carcinoma, and numerous others.

AMD3100 is proven to be effective, hence approved by the Food and Drug Administration (FDA) for the application in stem cell mobilization and radiation-induced injury.[24] AMD100 is no longer being developed for HIV-1 treatment, specifically as an antiretroviral therapy. This is due to the fact that it has failed to inhibit the infection of macrophage tropic (R5) HIV-1 strains, making it unsuitable for use as a monotherapy. Additionally, AMD100 has poor oral bioavailability and has been associated with serious side effects, such as cardiac disturbance. A clinical study was halted when it was discovered that extended use of AMD3100 caused premature ventricular contractions in 2 out of 40 patients.[24-28]

AMD070

AMD070, also referred to as AMD11070 or Mavorixafor, is a potent inhibitor of CXCR4, a protein involved in HIV-1 replication. It has a high level of tolerance and may be taken orally, making it an effective blocker of X4 HIV-1 replication. In a prior study, it was found that AMD070 significantly decreased the migration and invasion of oral cancer cells that rely on the CXCL12/CXCR4 pathway. In addition, it was shown that the combination of AMD070 and the light-absorbing material indocyanine green (ICG) created nanobubbles that hindered the interaction between CXCL12 and CXCR4 in breast cancer cells. As a result, this limited the growth of cancer cells and promoted programmed cell death, known as apoptosis.[26]

The pharmacological profile of AMD070 also showed potent inhibition of X4 HIV-1 replication and the gp120/CXCR4 interaction, which are crucial steps in HIV infection process. By inhibiting this interaction, AMD070 prevents HIV from entering CD4 cells, thus potentially inhibiting the progression of infection.[29]

Furthermore, AMD070 has demonstrated safety and efficacy in clinical trials for HIV-1 treatment. The fact that it has been tested in human clinical trials for this specific application and shown promising results is a strong indicator of its potential effectiveness. Safety in clinical trials is a critical factor, and demonstrating efficacy in this context is a clear signal of therapeutic potential.[30]

The clinical trial results for AMD070, known as AMD11070 in its trial phases, indicate its potential effectiveness in treating HIV-1 infection, particularly in patients harboring CXCR4-tropic virus. Within the tolerability and viral load reduction study conducted by Mosi et al. (2012), through clinical testing it was determined that the medicine exhibited good tolerability and was orally bioavailable in healthy volunteers. In a proof-of-concept clinical experiment including HIV-infected persons with X4 virus infection, 4 out of 9 patients experienced a reduction of more than 1log10 in X4 viral levels.[30]

MCo-CVX-5c

Next is MCo-CVX-5c, it is a cyclotide-based CXCR4 antagonist that Has demonstrated encouraging outcomes in impeding the penetration and duplication of CXCR4-tropic in human lymphocyte MT4 cells in a manner that is dependent on the dosage. Cyclotide analogs, including Mco-CVX-5c, have

become important lead candidates against CXCR4-mediated HIV-1 entry, it is shown to inhibit CXCL12-activation of CXCR4 and HIV infection by binding to CXCR4 with high affinity, thereby blocking the entry of HIV-1 into cells.[31]

Among all CXCR4 antagonists compared, MCo-CVX-5c provides the most recent research regarding its anti-HIV-1 activity. In addition to that, among the MCo-CVX-5c derivatives, MCo-CVX-PP is proven to have the highest potential as entry inhibitor in HIV-1 treatment since its IC_{50} value is 7.9 ± 0.5 nM being the most potent compared to its derivatives and AMD3100.[32]

BPRCX807

BPRCX807 exhibits greater efficacy compared to AMD3100, both when used as an individual drug and when combined with sorafenib, for antiangiogenic therapy. A research examining the use of a CXCR4 antagonist for treating hepatocellular carcinoma compared the benefits of BPRCX807 with the already licensed CXCR4 antagonist, AMD3100.

BPRCX807 exhibits a greater maximum tolerated dosage (MTD) in comparison to AMD3100 (75 mg/kg vs 15 mg/kg, respectively), indicating that BPRCX807 is much safer than AMD3100. Pharmacokinetic investigations have shown that BPRCX807 has significantly higher maximum concentration (Cmax) and blood exposure (area under the curve [AUC]) compared to AMD3100, demonstrating superior bioavailability and systemic exposure of BPRCX807.[33]

BPRCX807 has demonstrated the ability to hinder the formation of new blood vessels, enhance the infiltration of cytotoxic T cells, reduce the infiltration of tumor-associated macrophages (TAMs), and alter the polarization of TAMs in an orthotopic HCA-1 model. This leads to a transformation of the tumor microenvironment from immune suppression to anti-tumor immune response.

In addition to that, BPRCX807 exhibited exceptional selectivity for CXCR4, completely inhibiting its activity (100% inhibition), while only causing a minimal inhibition (5%) of other chemokine receptors. This indicates that BPRCX807 is a highly specific antagonist of CXCR4 with functional specificity. Ultimately, BPRCX807 has been proven to effectively hinder the movement of HCC cells through the CXCL12/CXCR4 axis, suggesting its potential to reduce metastasis.[34-35]

STRENGTH AND LIMITATION

The strength of this study is its ability to represent the HIV-1 cases trendline in Indonesia and the dominated strain, as well as the comprehensive comparison of host genetics and CXCR4 antagonists for HIV-1. The limitation of this study is the lack of available research conducted within the area of the developed clinical trials for the CXCR4 antagonists.

CONCLUSIONS

In conclusion, as HIV-1 cases keeps increasing especially in Indonesia with X4 strain dominating, CXCR4 antagonists that are highly potential for development and to further be utilized as HIV-1 antiretroviral therapy are AMD070 and MCo-CVX-5c.

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CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest.

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REFERENCES

1. Naranbhai V, Carrington M. Host genetic variation and HIV disease: from mapping to mechanism. Immunogenetics [Internet]. 2017; 69(8):489–98. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537324/
2. Chen B, S C, RB S, H V, SS S, A G. Molecular mechanism of HIV-1 entry. Trends Microbiol. 2019 Oct; 27(10):878–91.
3. Lopalco L. Tackling HIV: Genetic vs. immune CCR5 targeting. J AIDS Clin Res. 2014; 5(9).
4. González-Arriagada WA, García IE, Martínez-Flores R, Morales-Pison S, Coletta RD. Therapeutic perspectives of HIV-associated chemokine receptor (CCR5 and CXCR4) antagonists in carcinomas. Int J Mol Sci. 2022 Dec 28; 24(1):478–8.
5. Laporan Tahunan HIV/AIDS Tahun 2022 – Ditjen P2P Kemenkes RI [Internet]. Kemkes.go.id. 2022. Available from: https://p2p.kemkes.go.id/laporan-tahunan-hiv-aids/
6. Mulyani M, Ulfah RRM, Nurfitria RS. Incidence, prevalence, and pattern of tuberculosis treatment in HIV/AIDS patients in Regional General Hospital of Bandung City. J Community Health. 2019; 5(3).
7. Khairunisa SQ, Megasari NLA, Ueda S, Budiman W, Kotaki T, Nasronudin, et al. 2018–2019 update on the molecular epidemiology of HIV-1 in Indonesia. AIDS Res Hum Retroviruses. 2020 Nov 1; 36(11):957–63.
8. Indriati DW, Witaningrum AM, Yunifiar MQ, Khairunisa SQ, Ueda S, Kotaki T, et al. The dominance of CRF01_AE and the emergence of drug resistance mutations among antiretroviral therapy-experienced, HIV-1-infected individuals in Medan, Indonesia. Acta Med Indones. 2020; 52(4).
9. Khairunisa SQ, Megasari NLA, Ueda S, Kotaki T, Hidayati AN, Nasronudin, et al. Subtype distribution and drug resistance patterns among HIV-1 strains prevalent in Makassar, Indonesia. AIDS Res Hum Retroviruses. 2023; 39(3):124–9.
10. Selyutina A, Persaud M, Simons LM, Bulnes-Ramos A, Buffone C, Martinez-Lopez A, et al. Cyclophilin A prevents HIV-1 restriction in lymphocytes by blocking human TRIM5α binding to the viral core. Cell Rep [Internet]. 2020 Mar 17 [cited 2023 Dec 13]; 30(11):3766–3777.e6. Available from: https://www.sciencedirect.com/science/article/pii/S2211124720302746

11. Mamatis JE, Pellizzari-Delano IE, Gallardo-Flores CE, Colpitts CC. Emerging roles of cyclophilin A in regulating viral cloaking. Front Microbiol. 2022 Feb 15; 13.
12. Kim K, Dauphin A, Komurlu S, McCauley SM, Yurkovetskiy L, Carbone C, et al. Cyclophilin A protects HIV-1 from restriction by human TRIM5α. Nat Microbiol. 2019 Oct 21; 4(12):2044–51.
13. Chen F, Ke Q, Wei W, Cui L, Wang Y. Apolipoprotein E and viral infection: Risks and mechanisms. Mol Ther Nucleic Acids. 2023 Sep 1; 33:529–42.
14. Lunardi LW, Bragatte MA de S, Vieira GF. The influence of HLA/HIV genetics on the occurrence of elite controllers and a need for therapeutics geotargeting view. Braz J Infect Dis. 2021 Sep; 101619.
15. Mohamed H, Gurrola T, Berman R, Collins M, Sariyer IK, Nonnemacher MR, et al. Targeting CCR5 as a component of an HIV-1 therapeutic strategy. Front Immunol [Internet]. 2022 Jan 20; 12:816515. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8811197/
16. Henrich TJ, Hanhauser E, Harrison LJ, Palmer CD, Romero-Tejeda M, Jost S, et al. CCR5-Δ32 heterozygosity, HIV-1 reservoir size, and lymphocyte activation in individuals receiving long-term suppressive antiretroviral therapy. J Infect Dis. 2015 Oct 28; 213(5):766–70.
17. Latinovic OS, Reitz M, Heredia A. CCR5 inhibitors and HIV-1 infection. J AIDS HIV Treat. 2018 Dec 20; 11(1):1–5.
18. Vicenzi E, Liò P, Poli G. The puzzling role of CXCR4 in human immunodeficiency virus infection. Theranostics [Internet]. 2013 [cited 2019 Nov 5]; 3(1):18–25. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3563077/
19. Debnath B, Xu S, Grande F, Garofalo A, Neamati N. Small molecule inhibitors of CXCR4. Theranostics. 2013; 3(1):47–75.
20. Armani-Tourret M, Zhou Z, Gasser R, Staropoli I, Cantaloube-Ferrieu V, Benureau Y, et al. Mechanisms of HIV-1 evasion to the antiviral activity of chemokine CXCL12 indicate potential links with pathogenesis. PLOS Pathog. 2021 Apr 19; 17(4). doi:10.1371/journal.ppat.1009526.
21. Grande F, Occhiuzzi M, Rizzuti B, Ioele G, De Luca M, Tucci P, et al. CCR5/CXCR4 dual antagonism for the improvement of HIV infection therapy. Molecules. 2019 Feb 2; 24(3):550.
22. Guo J, Yan Y, Zhang JF, Ji J, Ge Z, Ge R, et al. Co-receptor tropism and genetic characteristics of the V3 regions in variants of antiretroviral-naive HIV-1 infected subjects. Epidemiol Infect. 2019 Jan 1; 147.
23. Walenkamp AME, Lapa C, Herrmann K, Wester HJ. CXCR4 ligands: The next big hit? J Nucl Med [Internet]. 2017 Sep 1; 58(Suppl 2):77S–82S. Available from: https://jnm.snmjournals.org/content/58/Supplement_2/77S
24. Wang J, Tannous BA, Poznansky MC, Chen H. CXCR4 antagonist AMD3100 (plerixafor): From an impurity to a therapeutic agent. Pharmacol Res. 2020 Sep; 159:105010.

25. Huang LSM, Snyder EY, Schooley RT. Strategies and progress in CXCR4-targeted anti-human immunodeficiency virus (HIV) therapeutic development. Clin Infect Dis. 2021 Sep 7; 73(5):919–24.
26. Zhao R, Liu J, Li Z, Zhang W, Wang F, Zhang B. Recent advances in CXCL12/CXCR4 antagonists and nano-based drug delivery systems for cancer therapy. Pharmaceutics [Internet]. 2022 Jul 25; 14(8):1541. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9332179/
27. Galsky MD, Vogelzang NJ, Conkling P, Raddad E, Polzer J, Roberson S, et al. A phase I trial of LY2510924, a CXCR4 peptide antagonist, in patients with advanced cancer. Clin Cancer Res. 2014 Jun 30; 20(13):3581–8.
28. Fricker SP. Physiology and pharmacology of plerixafor. Transfus Med Hemother. 2013; 40(4):237–45.
29. Uchida D, Kuribayashi N, Kinouchi M, Sawatani Y, Shimura M, Mori T, et al. Effect of a novel orally bioavailable CXCR4 inhibitor, AMD070, on the metastasis of oral cancer cells. Oncol Rep. 2018 Apr 25.
30. De Clercq E. Mozobil® (plerixafor, AMD3100), 10 years after its approval by the US Food and Drug Administration. Antivir Chem Chemother. 2019 Jan; 27:204020661982938.
31. Zhang C, Zhu R, Cao Q, Yang X, Huang Z, An J. Discoveries and developments of CXCR4-targeted HIV-1 entry inhibitors. Exp Biol Med. 2020 Feb 4;245(5):477–85.
32. Chaudhuri D, Lu T, Jacob B, Abraham S, Shankar P, Poss MA, et al. Lipidation of a bioactive cyclotide-based CXCR4 antagonist greatly improves its pharmacokinetic profile in vivo. J Control Release. 2023 Jul 1; 359:26–32.
33. Song JS, Chang CC, Wu CH, Dinh TK, Jan JJ, Huang KW, et al. A highly selective and potent CXCR4 antagonist for hepatocellular carcinoma treatment. Proc Natl Acad Sci. 2021 Mar 22; 118(13):e2015433118.
34. Dogra N, Jakhmola R, Potshangbam AM, Buch S, Katare DP. CXCR4 as possible druggable target linking inflammatory bowel disease and Parkinson's disease. Metab Brain Dis. 2023 Jan 19; 38(3):1079–9
35. Agosto LM, Zhong P, Munro J, Mothes W. Highly active antiretroviral therapies are effective against HIV-1 cell-to-cell transmission. PLoS Pathog. 2014 Feb 27; 10(2):e1003982.