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"DEVELOPMENT FOR RECENT THERAPY THE DISEASE OF HIV/AIDS"

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ABSTRACT :

Antiretroviral therapy is the term for the medication-assisted treatment of HIV (ART). It entails taking a variety of medications daily. ART is advised for all HIV-positive individuals. The medications prolong and improve the quality of life for those living with HIV, but they do not cure the virus.Since 2018, there have been more antiretroviral (ARV) medications accessible for the treatment of HIV.New kinds of antiretrovirals (ARVs) with different mechanisms of action, such Fostemsavir, have been approved. The name for medication-assisted treatment of HIV is antiretroviral therapy (ART). It means taking multiple medications on a daily basis. For everyone who is HIV positive, ART is recommended. The drugs do not cure HIV; instead, they extend and enhance the quality of life for persons who are infected.Antiretroviral (ARV) drugs are now more widely available for the treatment of HIV since 2018.New classes of antiretrovirals (ARVs) have been licensed, such as Fostemsavir, which have different mechanisms of action.

Keywords: **Antiretroviral therapy, HIV infection, Novel types of ARVs, Fostemsavir, Bacterivore, Emtricitabine, Tenofovir, Alafenamide, Combination antiretroviral therapy.**

I.INTRODUCTION

HIV stands for human immunodeficiency virus. AIDS stands for acquired immunodeficiency syndrome. HIV H: People, not animals, are the only hosts and carriers of this virus. Bites from mosquitoes, bats, or other animals cannot spread it. I. Our bodies' immune systems protect us from infections, illnesses, and other dangers. HIV-positive people, however, are unable to fend off infections. But there is a weakening of the immune system. The V-virus is a little, uncomplicated thing that is present outside the body in an inactive condition before entering the body and becoming active. AIDS A cannot be passed down over generations because it is not inherited. It is transferred from sick people to healthy people. There is a weakened immune system. HIV is the virus that causes AIDS. Normally, the immune system in our bodies fights bacteria and viruses. Our immune system's white blood cells protect us from infections. White blood cells contain helper cells, often known as T cells or CD4+ cells. An infected person will be able to proliferate. These infections prey on the body's immune system. These infections may cause a variety of illnesses, including death. HIV is the virus that causes AIDS. Normally, the immune system in our bodies fights bacteria and viruses. Our immune system's white blood cells protect us from infections. White blood cells contain helper cells, often known as T cells or CD4+ cells. There is a weakened immune system. D-Generates an immune system devoid of CD4+ cells. S-It is a collection of ailments. HIV is the virus that causes AIDS. Normally, the immune system in our bodies fights bacteria and viruses. Our immune system's white blood cells protect us from infections. White blood cells contain helper cells, often known as T cells or CD4+ cells. An infected person will be able to spread. These infections prey on the body's immune system. These infections may cause a variety of illnesses, including death. HIV is unable to resist disease, and when it does, its CD4 cell count decreases. While there is no known cure for AIDS, a number of drugs can be helpful. HIV is unable to resist disease, and when it does, its CD4 cell count decreases. While there is not a cure for AIDS, there are a number of drugs that can decrease the disease's progression and prolong your quality of life. Medication is not a cure for any disease [1]. HIV is the virus that causes AIDS. Normally, the immune system in our bodies fights bacteria and viruses. Our immune system's white blood cells protect us from infections. White blood cells contain helper cells, often known as T cells or CD4+ cells. An infected person will be able to proliferate. These infections attack on the body's immune system. .. These infections may cause a variety of illnesses, including death. HIV is unable to repress the disease, and when it does, its CD4 cell count decreases. While there is no known cure for AIDS, a number of drugs can be helpful. HIV is unable to repress the disease, and when it does, its CD4 cell count decreases. While there is no known cure for AIDS, there are a number of drugs that can decrease the disease's progression and prolong your quality of life. Medication is not a cure for any disease [1]. HIV is the virus that causes AIDS. Normally, the immune system in our bodies fights bacteria and viruses. White blood cells in our immune system shield us against pathogens. Helper cells, or T cells, or CD4+ cells are found in white blood cells. An infected individual will have the capacity to grow. These infections prey on the immunological system of the body. These infections result in a number of health issues, including death of patient HIV cannot fend off illnesses, and its CD4 cell count falls along with it. Although there isn't a cure for AIDS, several medications can help the disease progress more slowly and keep you healthier for longer. Medication is not a cure for diseases. HIV is unable to

fight off disease, and when it does, its CD4 cell count decreases. While there is no known cure for AIDS, there are a number of drugs that can decrease the disease's progression and prolong your quality of life. Medication is not a cure for diseases.HIV continues to be a serious global public health concern, having taken 40.4 million lives [32.9–51.3 million] to date and continuing to spread throughout all nations. Several nations have reported rising rates of new infections after years of decline. The virus known as human immunodeficiency virus (HIV) targets the immune system of the body. AIDS, or acquired immunodeficiency syndrome, is the disease's most advanced stage. HIV attacks white blood cells in the body, impairing immunity. This increases the risk of acquiring infections, some malignancies, and diseases like tuberculosis.(2,5)

II.PATHOPHYSIOLOGY

The only family of viruses that causes a lifelong infection is the Retroviridae, which reverse-transcribes the RNA viral genome into deoxyribonucleic acid (DNA) before merging into the host DNA. The most well-known pathophysiologic mechanism is that of HIV-1, although more recent research has made it easier to understand how the biology and replication of the HIV-2 and HTLV viruses differ from one another.

Since T cells and macrophages that express CD4 are the primary targets of HIV-1 and HIV-2, these cells serve as the primary host cellular receptors for these viruses. The envelope glycoprotein of the virus facilitates the virus's entry into the host cell. The viral and host cellular membranes merge as a result of the envelop protein's conformational change in reaction to chemokine coreceptors 5 (CCR5) and 4 (CXCR4) on the host cell surface. When the membranes fuse, the viral capsid is released into the host cell.

The HIV-1 viral capsid is entire, or almost whole, once it enters the nuclear pore complexes on the nuclear envelope of the host cell. It is currently believed that reverse transcription occurs during or shortly after the capsid is imported into the nucleus, contrary to the previous theory that it occurs in the cytoplasm. Reverse transcription is not as successful without the nuclear capsid. The precise location of reverse transcription, its mechanism, and the role of the capsid in all of this remain unknown.Certain molecular studies suggest that reverse transcription and uncoating originate in the nucleus. Conversely, some suggest that the host cell's nuclear envelope may be in close proximity to the site of the initial viral DNA synthesis and that the capsid may partially uncoat at nuclear pore complexes

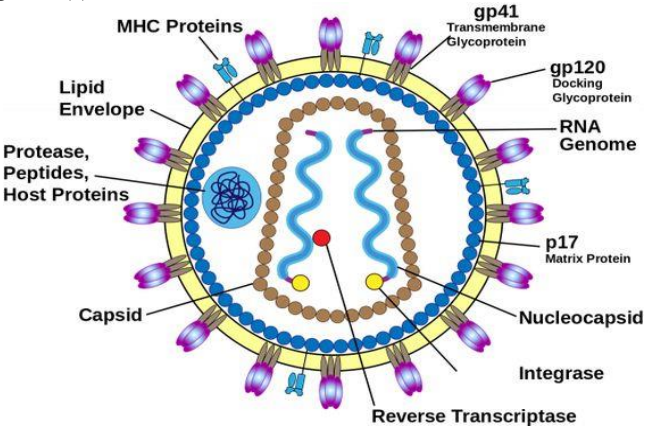
The viral reverse transcriptase enzyme initiates reverse transcription by using primers made of host transfer RNA, which bind at the 5' ends of the two identical RNA strands and continue in a 5' to 3' orientation. The viral genome first makes single-stranded DNA with a negative sense, but halfway through, the strands begin to double. Once elongation reaches the end of the genome, the remaining strands complete their synthesis by using the other as a template.[2] The viral integrase protein then randomly integrates the dsDNA into the host DNA.

The creation of viruses is not covered in this review. Once formed, viral particles can infect more host cells, so spreading the illness. Two days following the initial mucosal interaction, HIV can be detected in the tissue of the nearby lymph nodes. From this point on, the virus just needs three more days to manifest itself in the plasma.

Genomic diversification plays a major role in the pathophysiology of HIV infection, influencing the course of the disease and its response to antiretroviral therapy (ART). One of the primary reasons of HIV-1 mutagenesis is the error rate of the virus-encoded reverse transcriptase. Based on results from several studies, the error rate of HIV-1 group M reverse transcriptase (subtype B) is 100–1000 times higher than that of cellular DNA polymerases. These errors are incorporated into the viral genome and contribute to the virus's diversity. Due to extra intrinsic and extrinsic factors such recombination errors, host restriction factors, and host deoxynucleoside triphosphate depletion, viral mutagenesis and variety may cause ART failure.

In the early phases of the infection, viral replication is abundant due to the large number of susceptible CD4+ T cells and the absence of a host immune response, which causes the plasma HIV RNA level to rise exponentially. Then, there is a noticeable decline from the peak viremia level due to the HIV-specific immune response triggered by the cytotoxic CD8+ T cells. The first strong immune response and the symptoms that go along with it disappear after this decline, but HIV replication reaches a threshold where infection and continuous replication persist.

The precise processes that cause humoral immunity to break down are unknown. It is thought that T cells within B cell follicles, specifically the follicular T helper cells and follicular T regulatory cells, contribute to low humoral immunity and HIV persistence in patients receiving antiretroviral therapy (ART). Moreover, follicular CD8+ cytotoxic T cells are relatively less numerous in HIV-positive persons than their extrafollicular counterparts, which is thought to contribute to poor immunogenesis.(6)



STRUCTURE OF HIV

III.SYMPTOMS OF HIV

Symptoms related to acute HIV infection (when a person is first infected) can be similar to the flu or other viral illnesses.They include:

- Fever and muscle pains
- Headache
- Sore throat
- Night sweats
- Mouth sores,including yeast infection (thrush)
- Swollen lymph glands
- Diarrhea

Many people have no symptoms when they are first infected with HIV.

Acute HIV infection (Stage 1) progresses over a few weeks to months to become chronic or asymptomatic HIV infection (Stage 2) (no symptoms). This stage can last 10 years on longer.During this period, the person might have no reason to suspect they have HIV,but they can spread the virus to others.

Nearly all HIV-positive individuals will progress to Stage 3 AIDS if they do not receive treatment. After being infected, some people have AIDS within a few years. Others, referred to as long-term nonprogressors, are still in perfect health after ten or even twenty years.(10,11)

HIV has weakened the immune systems of those who have AIDS. They have a very high chance of contracting infections that are rare in healthy individuals.Any region of the body might be impacted by these illnesses, which are known as opportunistic infections.These can be caused by:

- Bacteria
- Viruses
- Fungi
- Protozoa

In addition, cancer risk increases are associated with AIDS, particularly lymphomas and Kaposisarcoma.(14)

The specific infection and the affected body part determine the symptoms. With AIDS, lung infections are common and can result in fever, coughing, and dyspnoea.(7)

Intestinal infections are also common and can cause:

- Diarrhoea
- Abdominal pain
- Vomiting
- Swallowing problems

IV.DIAGNOSIS

HIV can be diagnosed with quick diagnostic tests that deliver same-day findings. Early diagnosis and connection to therapy and prevention are considerably aided by this. HIV self-tests can also be used by individuals to test themselves. Nevertheless, confirmatory testing, carried out by a licensed and skilled health or community worker at a community centre or clinic, is necessary as no single test can provide a complete HIV positive diagnosis. Using WHO-prequalified assays within a nationally approved testing strategy and algorithm, HIV infection can be identified with high accuracy.The majority of commonly used HIV diagnostic tests identify the antibodies that an individual produces as part of their immunological response to combat HIV. Most HIV-positive individuals acquire antibodies within 28 days of infection. People are in what is known as the "window period" during this time, when their low antibody levels make it difficult for many quick tests to identify HIV in them but increase the risk of spreading the infection to others. After 28 days, those who test negative and have recently been exposed to a high-risk substance can undergo another test.

Before receiving treatment and care after a positive diagnosis, individuals should undergo another test to rule out any possible testing or reporting error. While testing has become more straightforward and effective for adults and adolescents, newborns born to HIV-positive mothers still do not have this option. Rapid antibody testing is insufficient for identifying HIV infection in children under the age of 18 months; virological testing should begin as early as birth or no later than six weeks of age. The ability to conduct this test at the point of care and provide same-day findings is now possible thanks to new technology, which will hasten the proper linkage with care and treatment.(10)

V.PREVENTION

HIV is a preventable disease. Reduce the risk of HIV infection by:

- using a male or female condom during sex
- being tested for HIV and sexually transmitted infections
- having a voluntary medical male circumcision
- using harm reduction services for people who inject and use drugs.

Doctors may suggest medicines and medical devices to help prevent HIV, including:

- antiretroviral drugs (ARVs), including oral PrEP and long acting products
- dapivirine vaginal rings
- injectable long acting cabotegravir.

ARVs can also be used to prevent mothers from passing HIV to their children.
People taking antiretroviral therapy (ART) and who have no evidence of virus in the blood will not pass HIV to their sexual partners. Access to testing and ART is an important part of preventing HIV.(6)

VI.WHO RESPONSE

In order to achieve the goals of ending AIDS, viral hepatitis B and C, and sexually transmitted infections by 2030, the health sector is guided in implementing strategically focused responses by global health sector strategies on HIV, viral hepatitis, and sexually transmitted infections for the period 2022–2030 (GHSSs).First foremost.(1)
The GHSS suggests coordinated and disease-specific national initiatives backed by initiatives from WHO and partners. They take into account the historical changes in epidemiology, technology, and context, encourage learning across the spectrum of diseases, and provide chances to use new insights and technologies to combat the diseases. They demand a targeted approach to reach the most vulnerable and impacted individuals for each condition that tackles disparities. They help to achieve the objectives of the 2030 Agenda for Sustainable Development by fostering synergies within the scope of primary healthcare and universal health coverage.

VII.CURRENT TREATMENT FOR HIV/AIDS

7.1.Promising Drugs in Development

HIV therapy has advanced significantly.Most HIV-positive individuals can lead regular lives with daily medicine.However, unfulfilled needs persist.For example, some people struggle to remember to take their medication on a daily basis.Some people acquire HIV strains that are resistant to drugs, rendering treatment ineffective. A new study found that using virus-like particles, people living with chronic HIV can effectively "shock and kill" their latent HIV reservoirs.By 2030, the World Health Organisation (WHO), the Global Fund, and UNAIDS want to see an end to the AIDS and HIV epidemic. An innovative therapy for AIDS has been proposed by a recent study from Tel Aviv University. This treatment might potentially be converted into a vaccine or used as a one-time treatment for HIV patients. The study looked at how the patient's body engineered type B white blood cells to release anti-HIV antibodies in reaction to the virus.

For adult patients with type 1 HIV, the U.S. Food and medicine Administration authorised Sunlenca (lenacapavir) on December 22, 2022. Sunlenca is a novel antiviral medicine.
Cabenuva, which was approved by the FDA in 2021, is a combination of two different HIV medications: cabotegravir and rilpivirine. You get it as an injection at your doctor's office either once a month or once every two months. For people who struggle to remember to take their meds on a regular basis, it makes things a lot easier. Only individuals who have achieved undetectable virus on current therapy are eligible for this drug.(24)
The FDA is almost ready to approve the drug islatravir. This class of drugs is known as nucleoside reverse transcriptase translocation inhibitors, or NRTTIs. The monthly drug, which is currently undergoing clinical trials, blocks a protein that promotes the virus's proliferation. As a result, the body's HIV levels drop. Furthermore, it seems that some drug-resistant strains of HIV are resistant to it.

7.2 HIV Vaccine

The development of a therapeutic HIV vaccine is ongoing. Therapeutic immunisations cure a disease, not prevent it. HIV-positive people would receive this therapeutic vaccination to strengthen their immune systems' ability to fight off the infection. Without the need for ART, it is envisaged that the immunisation would prevent HIV from turning into an AIDS-causing virus on its own.(21)

Developing an HIV vaccine has been difficult thus far. In order to induce the body to develop antibodies against a virus, the bulk of traditional vaccines involve weakened or dead viruses. But employing weakened HIV hasn't worked well in that way, and utilising a live virus is too dangerous.
Researchers may, however, be making progress on an alternative vaccination. T cells, a subset of immune cells, are primed by the HTI vaccine to target a specific area of the virus that allows for self-replication. In a short research including 45 individuals who received the immunisation, 40% of the patients were able to go 22 weeks without receiving antiretroviral medicine.

Researchers are currently looking at the vaccination and the experimental drug vesatolimod. This drug may boost the immune system's reaction to the immunisation, boosting its effectiveness or extending its duration of action in more people.

7.3.Gene Editing

Gene editing might be used as an additional HIV treatment strategy. Gene editing technology alters an organism's DNA. Gene editing research is ongoing for a number of inherited disorders, such as haemophilia, sickle cell disease, and cystic fibrosis. Currently, researchers are trying to use it to fight HIV. Early studies on animals suggest that the simian HIV virus may be neutralised by a type of genome editing called CRISPR. immunodeficiency virus (SIV), which is widespread in monkeys and other animals. Very early human clinical trials started at the end of 2021. In the tests, scientists use CRISPR technology to cut off the HIV that encircles cell DNA and makes treatment so difficult.

It is thought that, unlike ART, which is a lifelong medicine, a single CRISPR therapy can perhaps cure the sickness.(10,12)

FDA-Approved ARV Classes Before 2018

Drug Class	Mechanism of Action	First Approved Drug	Approval Date
Nucleoside reverse transcriptase inhibitors	Inhibit reverse transcriptase via chain termination	Zidovudine	March 19, 1987
Nonnucleoside reverse transcriptase inhibitors	Inhibit reverse transcriptase via direct binding and inactivation	Nevirapine	June 21, 1996
Protease inhibitors	Inhibit HIV protease, an enzyme necessary for catalytic cleavage of proteins needed for viral replication	Saquinavir	December 6, 1995
Fusion inhibitors	Block entrance of HIV into CD4 cells	Enfuvirtide	March 13, 2003
CCR5 antagonists	Block CCR5 receptors on CD4 cell surfaces, preventing HIV entrance	Maraviroc	August 6, 2007
Integrase inhibitors	Inhibit integrase, an enzyme necessary for integration of viral DNA into host cells	Raltegravir	October 12, 2007

New Combination Approvals

Generic Name	Brand Name	Mechanism(s) of Action	Indication	Dosing	Route of Administration	Approval Date
Bictegravir, emtricitabine, and tenofovir alafenamide	Biktarvy	INSTI/NRTI/ NRTI	Treatment of HIV-1 infection as a complete regimen	1 tablet by mouth daily	Oral	February 2018
Lamivudine and tenofovir disoproxil fumarate	Cimduo	NRTI/NRTI	In combination with other ARV for the treatment of HIV-1 in adults and pediatric patients weighing ≥35 kg	1 tablet by mouth daily	Oral	February 2018
Efavirenz, lamivudine, and tenofovir disoproxil fumarate	Symfi Lo	NNRTI/NRTI/ NRTI	Treatment of HIV-1 infection in adult patients weighing ≥35 kg	1 tablet by mouth daily	Oral	February 2018
Efavirenz, lamivudine, and tenofovir disoproxil fumarate	Symfi	NNRTI/ NRTI/NRTI	Treatment of HIV-1 infection in adult patients weighing ≥40 kg	1 tablet by mouth daily	Oral	March 2018
Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide	Symtuza	NNRTI/ BOOSTER/ NRTI/NRTI	Treatment of HIV-1 infection in adults and pediatric patients ≥40 kg	1 tablet by mouth daily	Oral	July 2018
Doravirine, lamivudine, and tenofovir disoproxil fumarate	Delstrigo	NNRTI/ NRTI/NRTI	Treatment of HIV-1 infection in adults	1 tablet by mouth daily	Oral	August 2018
Dolutegravir and lamivudine	Dovato	INSTI/NRTI	Treatment of HIV-1 infection in adults	1 tablet by mouth daily	Oral	April 2018

VIII. CONTRAINDICATION

The following contraindications are associated with HIV medications:

Abacavir: Patients with the HLA-B*5701 allele or prior hypersensitivity reaction to abacavir

Emtricitabine: Patients with previously demonstrated hypersensitivity to any of the components of the products

Lamivudine: Patients with a previous hypersensitivity reaction to lamivudine

TDF: Previous hypersensitivity or glomerular filtration rate less than 50

Zidovudine: Patients who have had potentially life-threatening allergic reactions (eg, anaphylaxis, Stevens-Johnson syndrome) to any of the components of the formulations

Efavirenz: Individuals who exhibit clinically severe hypersensitivity to any of the product's constituents (such as Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) should not use efavirenz with elbasvir and grazoprevir together.(20, 21)

Etravirine: Hypersensitivity **NVP** For use as occupational and nonoccupational postexposure prophylactic regimens, or in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment. Men or women with CD4 levels higher than 400 or more, as there is a higher chance of a hypersensitive reaction. Although mostly cholestatic, hepatotoxicity also has a hepatocellular pattern. After the first eight weeks of treatment, there have been reports of clinically evident hepatotoxicity in certain cases, however these cases can be severe and even deadly.

Rilpivirine: Not recommended for coadministration with any of the following: rabeprazole, pantoprazole, esomeprazole, lansoprazole, omeprazole, phenobarbital, phenytoin, rifampin, rifapentine, dexamethasone, and St. John's wort.

Atazanavir : Patients who have previously shown signs of clinically significant hypersensitivity (such as Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the formulation ingredients are at risk for severe and potentially fatal events if they concurrently take medications that heavily rely on CYP450 3A4 (CYP3A) or UDP Glucuronosyl transferase Family 1 Member A1 (UGT1A1) for clearance. Atazanavir, when taken with medications that strongly induce CYP3A4, may result in decreased exposure and diminished efficacy of formulations.

Darunavir: Coadministration of formulations is contraindicated with medications highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and life-threatening events.

Fosamprenavir: In patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome), to any of the components of this product or amprenavir; when coadministered with medications that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and life-threatening events.

Ritonavir: Contraindicated in patients with known hypersensitivity, for example, toxic epidermal necrolysis or Stevens-Johnson syndrome, to ritonavir or any of its ingredients. Ritonavir is contraindicated with medications highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and life-threatening reactions. It is also contraindicated with drugs that are potent CYP3A inducers, where significantly reduced lopinavir plasma concentrations may correlate with the potential for loss of virologic response and possible resistance and cross-resistance.

Saquinavir: Contraindicated in those with congenital long QT syndrome, those with refractory hypokalemia or hypomagnesemia, and with concurrent administration with drugs that increase saquinavir plasma concentrations and prolong the QT interval. It is also contraindicated in people with complete atrioventricular block without implanted pacemakers or patients at high risk of complete atrioventricular block. In addition, it is contraindicated in patients with clinically significant hypersensitivity (eg,anaphylactic reaction, Stevens-Johnson syndrome) to saquinavir, saquinavir mesylate, or any of its ingredients; in patients with severe hepatic impairment. It is also contraindicated with drugs that are CYP3A substrates, for which increased plasma levels may result in serious or life-threatening reactions.

Tipranavir: Use of tipranavir is contraindicated with concurrent administration of drugs highly dependent on CYP3A4 for clearance or potent CYP3A4 inducers due to increased risk of intracranial bleeding. Tipranavir is also contradicted in moderate to severe hepatic impairment.(18,19)

Enfuvirtide: Known hypersensitivity to enfuvirtide or any of its components

Maraviroc: This drug is contraindicated in patients with severe renal impairment or end-stage renal disease (CrCl <30 mL per minute) who concomitantly take potent CYP3A inhibitors or inducers.

Dolutegravir: Previous hypersensitivity reaction to dolutegravir or receiving dofetilide due to the potential for higher dofetilide plasma concentrations and the risk for severe and life-threatening events

Raltegravir: None

Ibalizumab: None

Cobicistat: The concomitant use of cobicistat with atazanavir is contraindicated with drugs dependent on CYP3A or UGT1A1 for clearance and for which elevated plasma concentrations of the interacting drugs are due to serious life-threatening events. Darunavir and cobicistat should not be coadministered with drugs highly dependent on CYP3A for clearance, which may lead to increased plasma concentrations and life-threatening events.(20,21)

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