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# A Review on: HIV Therapy – The Influence of New Drugs

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**ABSTRACT:** The discovery of the human immunodeficiency virus (HIV) as the causative organism of acquired immunodeficiency syndrome (AIDS) and the inability of modern medicine to find a cure for it have placed HIV as the one of the most dreaded pathogens of the 21st century. With millions of people infected with HIV, it was once thought to result in “medical apocalypse”. However, with the advent of antiretroviral therapy (ART), it was now possible to control HIV. Adherence to ART helps to keep the viral load under control and prolong the time of progression to AIDS, resulting in near normal life expectancy. Even with the introduction of ART, a substantial number of patients fail to adhere due to a variety of reasons, including adverse effects, drug abuse, mental disorders, socioeconomic status, literacy, and social stigma. With the availability of so many options for HIV treatment at each stage of the disease progression, physicians can switch between the treatment regimens to avoid and minimize the adverse effects of drugs. Close monitoring, major social reforms, and adequate counselling should also be implemented to circumvent other challenges.

Categories: Infectious disease, Allergy/Immunology, HIV/AIDS

**KEYWORDS:** HIV, AIDS, drug adverse effects, HIV/AIDS, highly active antiretroviral therapy (HAART), antiretroviral therapy.

## I. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a medical condition caused by the human immunodeficiency virus (HIV). HIV infection is a very current threat and can easily be termed as a course upon the human race. The scientific community first noticed and recognized the presence of AIDS as an actual disease following an increase in the incidence of very rare opportunistic infections and cancers among otherwise healthy homosexual men (Accessed: December 28, 2015). HIV -1 was identified as the causative organism soon after the first official recognition of HIV patients in the USA. HIV-2 was reported first in Africa in 1985 and is markedly different from HIV-1. It closely resembles a simian virus that infects macaques in capacity. Simian viruses that naturally infect Africa primates are suspected to reach humans via multiple cross-species transmissions resulting in the spread of HIV-1 and HIV-2. The global prevalence of HIV has expanded since its discovery and has now spread across the globe despite advances in antiretroviral treatment (ART). The mortality and morbidity rates related to HIV infections remain high in developing countries largely due to food insecurity and malnutrition. Long term concomitant sexual relationships and high infectivity during the early phase of HIV infections are other factors behind the extensive spread of HIV in the general population (Tadesse WT: BMC Pharmacol Toxicol. 2014, 15:32.).

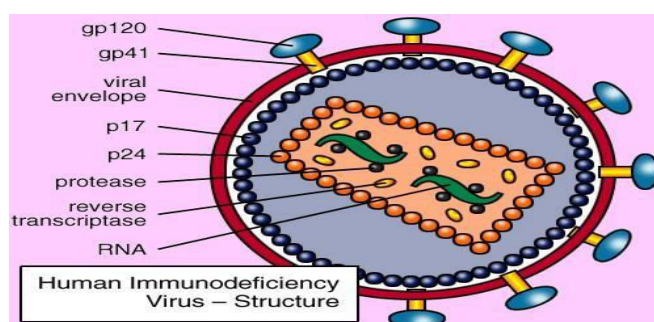
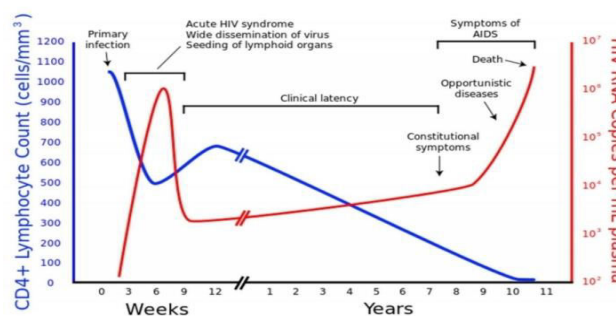


Fig.1: Structure of HIV Virus

## II. THE INFECTION

The main site of the attack is the immune system, especially the CD4 T-lymphocytes (CD4 cells). Once infected, the virus gradually and silently overpowers the host's defence mechanism, resulting in opportunistic infections and cancers that are otherwise rare. Activated and differentiated CD4 cells have a pivotal role in the activation of cell-mediated and humoral immune systems (AIDS behave.2011, 15:687-92). HIV infection results in the depletion continue over a course of several years until the patient succumbs to AIDS. It is the last stage of the HIV infection, and it presents itself anywhere between two and 15 years post infection. The following figure represents the timeline of HIV infection from initial infection to the expression of AIDS defining symptoms (figure2:).(Garnett GP: Concurrent sexual partnership and primary HIV infection A critical interaction).



### HIV SUBGROUP

#### HIV-1

HIV-1 is well-known for its extensive genetic diversity. There are four different lineages coming under HIV-1: M, N, O, and P. The most commonly reported HIV virus across the globe is group M. Group N less prevalent, reported only from Cameroon. Group P is the rarest of all and has been identified in Cameroon pregnant women in France. It has a prevalence of 0.06% of total HIV infections (AIDS behave.2011, 15:698).

#### Current status of HIV infection and mortality rate

Western, Central Europe, and North America

Approximately 2.4 million individuals are HIV-positive in this region. An estimated 102,000 new HIV infections were reported in 2019, and more than 50% of infections were from the USA. About 36,000 AIDS related deaths were also reported in the same period.(Eaton JW: Concurrent sexual partnership and primary HIV infection A critical interaction).

#### Asia and Pacific

As of 2019, approximately six million individuals were previously infected in Asia and the Pacific, with as many as 430,400 new HIV infections arising that year. China, Indonesia, and India contribute to about 78% of the total new disease burden in Asia and the Pacific with about 340,000 deaths. Patients receiving ART are approximately 36%, with 4.2 million active HIV patients having no access to ART (Tadesse YT: Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy).

Nationally, there were an estimated 20.52 thousand pregnant women who would require ART to prevent mother-to-child transmission of HIV.(HIV/AIDS Accessed: December 6, 2015).

#### 1. India

- As per recently released, India HIV estimation 2019 report, overall, the estimated adult (15-49 years) HIV prevalence trend has been declining in India since the epidemic peak in the year 2000 and has been stabilizing in recent years. The estimate for this indicator was 0.22% (0.17-0.29%) in 2019. In the same year, HIV prevalence among adult males was estimated at 0.24% and among adult female at 0.20%.
- Nationally, there were 69.22 thousand estimated new HIV infections in 2019. This translates into 190 new infections every day and eight new infections every hour.
- Nationally, 58.96 thousand AIDS related deaths were estimated in the year 2019.

### How is HIV Spread

#### 5. Sexual intercourse

HIV can be found in the semen and vaginal fluids of a person who is HIV infected. He or she can pass HIV onto another person through unprotected sex (not using a condom) vaginal, oral and anal sex.

#### 6. Pregnancy

HIV may be passed onto a baby from an HIV positive mother. Not all HIV positive mothers give birth to babies on HIV to the babies' increases if the mother is sick with an AIDS illness or if the mother gets infected with HIV during pregnancy.

HIV can pass to the baby during:

- The pregnancy
- At the time of delivery
- In breast milk

Many women only find out they have HIV when fall pregnant. By this time the unborn child is at risk of getting HIV. The chances of HIV passing from mother to child are between 20% and 40% during pregnancy and at the time of delivery. The risk of infection increases if the mother breast feeds. There are now medicines available to help reduce the spread of HIV to the baby.

#### 7. Blood

HIV can pass from one person to another through his or her blood. Sometimes sick people are given extra blood through a blood transfusion. In India are safe because blood is tested before it is given to sick people.

HIV can be passed on in very small amounts of blood, for example when people share razor blades which are not cleaned properly.

HIV can also be passed on by injection drugs and sharing needles.

People most at risk of this happening are:

- Injecting drug users
- Doctors and nurses treating with HIV.

HIV can also be pass on when handling blood without gloves, e.g. after an accident, as this blood may contain the HIV germ that could enter cuts and open wounds (Plantier: A new immunodeficiency virus derived from gorillas. Nat. Med.2009).

#### Agree that you cannot get HIV from:

- Eating food prepared by someone by with HIV
- Sharing cups, mugs, plates, food, spoons, forks etc.
- Door handles or rails
- Sneezing or coughing
- Tears or saliva
- Toilet seats
- Holding or shaking hands
- Mosquitoes
- Swimming pools or baths
- Working or attending school with someone who is HIV positive
- Donating blood
- Living with someone who has HIV
- Being next to or close to someone who has HIV
- Kissing, hugging or touching.

(M, Rowland-Jones SL: HIV-2: The forgotten AIDS virus .Trends microbial.2008).

### Symptoms of HIV infection

#### What are the symptoms of HIV infection?

Within a month or two of getting infected with HIV, many people (but not all) can develop flu-like symptoms, swollen glands or a rash. These symptoms usually go away within a couple of weeks, and a person can look and feel well for many years before the symptoms come back.

This period when you look and feel well can last five to seven years or longer in adults and two to five years or longer in children born with HIV. As HIV continues to attack the immune system, the illnesses start to show again (Ishikawa K, west Africa. 2001).

### **What will happen when someone with HIV gets sick?**

It can take many years for HIV to make you sick. When you start to feel sick because of serious infections, it means that you may have AIDS. Some early signs include: painful skin rashes (shingles), sores on the lips which do not heal, thrush (a white rash inside the mouth or on the private parts), and swelling in the neck, behind the ear, under the arm and in the groin. Signs and symptoms of TB include coughs, sweating and weight loss, fevers and sweating at night, as well as enlarged glands (Simbayi LC, Soc.Sci.Med.2007,64:1823-31).

### **Later signs of AIDS**

You can also develop any of the following problems when you get very sick with AIDS: TB, bad cough and fever (pneumonia), ‘pins and needles’ and pains in the hands and feet, diarrhoea that does not stop, weakness and tiredness, tumours on the skin, losing weight, headaches, seizure, black-outs, loss of memory, difficulty in concentrating and difficulty in swallowing (UNAIDS: Fact sheet 2015).

### **How will I know that I have HIV?**

You can look and feel healthy for years when you first have HIV in your body. There is only one way to find out whether you are living with HIV - by having an HIV test.

### **Should I have an HIV test?**

Find out as early as possible after being infected with HIV is important. This way you can get help and avoid spreading HIV without knowing it.

### **Why must I have an HIV test?**

- Knowing the result can reduce the stress and uncertainty of not knowing. Your doctor or clinic will be able to tell you if worrying signs and symptoms are HIV/AIDS-related.
- You cannot lose your job just because you are HIV positive – there are laws to protect you.
- You can change your lifestyle to protect sexual partners from future infections, so that you do not infect your sexual partner with the virus without knowing.
- Decisions about having children or entering into new relationships can be considered.
- A lot can be done to help you lead a healthy, normal life and slow down the time to developing AIDS if HIV is found early (before getting sick) in your blood.
- If you are HIV positive and register with Aid for AIDS, approval can be provided for multivitamins and preventative vaccinations to help you remain healthy.

### **How do I have an HIV test?**

- You should go to a clinic if you are thinking about having an HIV test. The health worker should sit down and talk to you about the test. You can decide whether or not to have the test. No one can force you to have an HIV test – it is your choice. If you decide to test, the health worker will take a blood or saliva (spit) sample. This will be checked for HIV antibodies, which are made by the immune system soon after you are infected. Some of the tests will give the results within a few minutes, but other tests need to be sent away to get the results. If your test has been sent away you will need to visit the health worker about one week later to get the result. If antibodies are found you have a ‘positive test’ and are infected with HIV. This is why people living with HIV are often called ‘HIV positive’ (WHO: Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV, 2015).

## **TREATMENT OF AIDS**

### **What are my rights?**

You have to decide whether to go for the test. Nobody, not even a doctor or your employer, has the right to force you to have the test without your permission. The test result is confidential. It is against the law for the health worker to tell someone else the result without your permission. It is important that the health worker explains the meaning of the test to you so you can decide if you want it.

“Aid for AIDS can help you lead a healthy, normal life”

### **Should I have counselling when going for an HIV test?**

Taking an HIV test is very personal and the test result can be difficult to handle. It is important to get counselling to prepare yourself for the test result. Try a local counselling centre or your local ATICC (AIDS Training, Information and Counselling Centre), if you do not know where to find one.

### **What if my HIV test is positive?**

- You are infected with HIV.
- You can spread it to your sexual partners if you have unsafe sex.
- You must always use a condom if you have sex.
- It is important to tell sexual partners that you are HIV positive. Discuss this with a counsellor or health worker.
- You must not donate blood. Pregnant women who are HIV positive may infect their babies. Not all babies will be infected with HIV. HIV can also be passed on during breast-feeding. The test cannot tell when you got the infection or when you will get sick (MMWR Morb Mortal Wkly Rep. 1981, 30:305–308).

### **What if the HIV test is negative?**

- No HIV has been detected in your blood.
- You may not have HIV if the test is negative. However, it may be necessary to test again. You could be in the 'window period', which is the time between when you are infected with HIV and the tests used by doctors and clinics become positive. This is usually two to four weeks (Sharp PM, Hahn B H: Origins of HIV and the AIDS pandemic).

"If you are HIV negative, keep yourself safe from HIV in the future. The key is to stay negative!"

### **Preventing the spread of HIV**

#### **How do I stop myself from being infected with HIV?**

"There is no cure for HIV. Once a person has HIV, they will remain infected for the rest of their life. Therefore preventing the spread is the most important way of controlling HIV"

#### **The following actions will prevent the spread of HIV:**

Protected sex – with a condom, used correctly.

- Sex without penetration – this is when a man's penis does not enter the woman's vagina or anus. This is also safe sex. Sex can be a way of showing love but not the only way. You can also show love by kissing, touching and holding each other.
- You can have sexual climax without penetration by rubbing the person's private parts with hands or fingers.
- It is important to reduce the number of different sexual partners.
- New relationships – you should use a condom. Both of you should go for an HIV test before you stop using condoms. It is safe to have sex without protection if both HIV tests are negative. This means you are both free of HIV.
- Remember that both partners must stay in a sexually faithful relationship with only each other; otherwise the sex will no longer be safe. This is a faithful relationship (Sharp PM: Serological evidence for virus related to simian T-lymphotropic retrovirus in residents of West Africa Lancet. 1985;2:1387-8).

### **Sexually transmitted infections**

#### **How do I get my partner to agree to have protected sex?**

One of the reasons why HIV is spreading so fast is that many people do not want to talk about sex. The key here is communication. You should have open discussions about having an HIV test, using condoms, being faithful and the dangers of unsafe sex. Discussion about sex and relationships with your partner needs to happen if you are going to protect yourself from HIV. If you are unsure of how to deal with this, contact the National AIDS Helpline, your local ATICC (AIDS, Training, Information and Counselling Centre) or Aid for AIDS (Eaton JW: A critical interaction. AIDS Behav. 2011, 15:687–92).

#### **"Have open talks with your partner"**

#### **Sexually Transmitted Infections can increase the chance of HIV infection**

Any sickness passed on from one person to another during sex. Gonorrhoea, the drop, syphilis and herpes are STIs. A person with an STI may have a discharge or sores on his or her private parts. This makes it easier for the HIV to get into blood and the body during sex. STIs can be very dangerous and can cause bad infections and HIV can get into your body and blood more easily through broken skin if you already have an STI. This means that HIV can be spread from one person to another more easily.

### How do I know if I have a sexually Transmitted Infection

- Sores on your genitals or anus
- White, yellow or green discharge from your penis or vagina
- Pain in the lower stomach
- Burning or pain when going to the toilet
- Itching or redness around the private parts
- Painful sex
- Pain in the testicles
- Swelling in the groin

It is important that you have an STI treated. Clinics and doctors can treat STIs with tablets or with an injection. Treatment of STIs usually works quickly (Watson R:Wageningen, Netherlands; 2015. 10:537–562).

**“STIs are passed on during unprotected sex”**

### Living with HIV/AIDS

**I have heard that you cannot treat people who have HIV or AIDS? What should I do to stay healthy if I am HIV positive?**

Although there is no cure for HIV, there is a lot that can be done to lead a healthy and ‘normal’ life. Good medical care and hygiene can do a lot to keep people well for a long time and lengthen the time before you get sick and develop AIDS.

• Register on the Aid for AIDS programme if you are a member of a contracted medical scheme or company (they are there to assist you). Contact the programme on 0860 100 646.

- Stay working and active for as long as possible.
- Have protected or safe sex (correctly using a condom).
- Visit the doctor or hospital for regular checkups.
- Eat good food and stay strong for as long as possible.

### Improve your lifestyle by keeping healthy, including:

- Exercise regularly.
- Eat a healthy balanced diet (vegetables, beans, eggs and fruit).
- Stop smoking and avoid alcohol. (These things make your body weak so it is easier for HIV to get strong and you to get AIDS earlier.)
- Medication can help slow down HIV, the disease and to prevent illnesses.
- Get enough rest and reduce stress levels.
- Take multivitamins.
- Drink lots of water.

(Dellar R, Karim QA: HIV/AIDS food insecurity, and undernourishment).

**“Stay healthy!”**

### Treatments options for HIV

HIV infection has a very complex pathogenesis and varies substantially in different patients. Therefore, it can easily be considered as a very host-specific infection. The specificity of pathogenesis often complicates treatment options that are currently available for HIV infection. Effective management of HIV infection is possible using different combinations of available drugs. This method of treatment is collectively known as antiretroviral therapy (ART). Standard ART is comprised of a concoction of at least three medicines (termed as “highly active antiretroviral therapy” or HAART). Effective ART often helps control the multiplication of HIV in infected patients and increases the count of CD4 cells, thus, prolonging the asymptomatic phase of infection, slowing the progression of the disease, and also helps in reducing the risk of transmission (Luckheeram RV, Xia B: CD4+T cells:2015).

### FDA-approved HIV drug classes

#### Reverse Transcriptase Inhibitors

Reverse transcriptase inhibitors are a group of drugs, which can bind and inhibit the reverse transcriptase enzyme to intercept the multiplication of HIV. There are two types of inhibitors: non-nucleoside reverse transcriptase inhibitors

(NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTI). Examples of this group of drugs include zidovudine, didanosine, abacavir, tenofovir, and Combivir.

#### **Protease Inhibitor**

Regulation of HIV protease is of high importance for the correct assembly and production of HIV. Protease inhibitors effectively block the functioning of protease enzymes in acutely and chronically HIV-infected CD4 cells. Inhibition of HIV protease enzymes results in the liberation of immature and non-infectious viral particles. Examples of this group of drugs include lopinavir/ritonavir, indinavir, ritonavir, nelfinavir, and amprenavir.

#### **Fusion Inhibitors**

This class of drugs acts by blocking HIV from entering the CD4 cells of infected patients. They inhibit the fusion of HIV particles with the CD4 cells. Enfuvirtide is an example of a fusion inhibitor used in HIV treatment.

#### **Chemokine Receptor 5 Antagonist**

This group of drugs prevents the infection by blocking the chemokine receptor 5 (CCR5) antagonist receptor present on CD4 cells. In the absence of vacant CCR5 receptors, HIV fails to gain entry and infect the cell. Maraviroc is an example of a CCR5 antagonist used in HIV treatment.

#### **Integrase Strand Transfer Inhibitors**

Strand transfer inhibitors prevent the integration of viral DNA into the host genome of CD4 cells by an integrase enzyme. Blocking integrase prevents HIV from replicating. Raltegravir, elvitegravir, and dolutegravir are some medications in this category.

#### **Treatment regimen for HIV**

Present HIV treatment guidelines recommend ART treatment for all patients, irrespective of the CD4 cell count, to improve and prolong the progression of disease to AIDS. Adherence to treatment is of paramount importance in order to achieve the full efficacy of treatment and also to prevent the incidence of drug resistance (Brenchley JM, Douek DC: CD4-2013).

#### **Latest WHO recommendations for ART**

A concise form of 1st, 2nd, and third line treatment options recommended by the World Health Organization (WHO) is given below.

#### **First-line ART**

Adults: First-line ART treatment for adults consists of two NRTIs and one NNRTI. Tenofovir disoproxil fumarate (TDF) + lamivudine (3TC) or emtricitabine (FTC) + efavirenz (EFV) as a fixed dose is the favoured choice for this type of ART. When this drug combination is contraindicated or is unavailable, 1) zidovudine (AZT) + 3TC + EFV, 2) AZT + 3TC + nevirapine (NVP), or 3) TDF + 3TC (or FTC) + NVP is used ( Moss AR, Bacchetti P: Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. Br Med J. 1988).

#### **Contraindications:**

1. Creatinine clearance is less than 50 ml per minute: Tenofovir.
2. Patients on psychoactive drug treatment: Efavirenz.
3. Patients who are pregnant or who are trying to conceive: Efavirenz.
4. ALT elevation: Nevirapine.

#### **Pregnant and breastfeeding patients:**

First-line ART in this subpopulation is comprised of a single daily dose of TDF + 3TC (or FTC) + NVP. Breastfeeding infants of mothers who are receiving ART must receive six weeks of infant prophylaxis with a daily dose of NVP. The preventive medication should commence immediately post-delivery or when HIV exposure is identified.

#### **Pediatric patients:**

Patients below three years of age should be given Lopinavir/Ritonavir (LPV/r)-based treatment, even under NNRTI exposure. When LPV/r is not a viable option, NVP based treatment should be used. For infected children who are over age three, EFV is the ideal NNRTI while NVP has been identified as the second option. For infected children younger

than three years of age, who develop TB while on the Lopinavir/Ritonavir (LPV/r)-based treatment, the NRTI regimen should be switched to abacavir (ABC) + 3TC or AZT + 3TC until the TB infection is cleared. NRTI regimens similar to that of adults (TDF + 3TC (or FTC)) or (AZT + 3TC) or (ABC + 3TC) are preferred for patients between 10 and 19 years of age who weigh 35 kg or more (Vallari A: Prevalence continues to be low. AIDS Res Hum Retroviruses. 2010).

#### Second-line ART

Adults, including pregnant and breastfeeding patients: When a first-line treatment of ART fails, a second-line ART should be utilized. The second-line ART is comprised primarily of two NRTIs and a Ritonavir-boosted PI. The recommended option for second-line ART includes AZT and 3TC as the NRTI. After the failure of AZT or stavudine (d4T) + 3TC based first-line regimen, TDF + 3TC (or FTC) as the NRTI should be considered. When first-line NNRTI-based treatment fails, two NRTIs + a boosted PI are suggested

#### Pediatric patients:

For children below three years of age, first-line ART is continued even when it fails. No change in treatment is recommended; instead, adequate steps should be taken to improve adherence to the ART regimen. If first-line ART fails in children ages three and up, a second-line treatment consisting of one NNRTI and two NRTIs should be given. If ABC or TDF + 3TC (or FTC) fails, the recommended option is AZT + 3TC. After a failure of AZT or d4T + 3TC (or FTC) in first-line treatment, the preferred NRTI option is ABC or TDF + 3TC (or FTC).

#### Third-line ART

If first- and second-line ART fails, the WHO recommends inclusion of new medicines with the least amount of risk for development of cross-resistance towards previously used drugs (e.g. integrase inhibitors and second-generation NNRTIs and PIs).

#### Factors to consider when selecting ART

The major factors that deserve thorough consideration while choosing an ART for a patient include the viral load and CD4 cell count before the treatment, the result of HIV genotypic drug resistance test, HLA-B\*5701 status, patient preferences, and anticipated adherence. Comorbid conditions to screen prior to ART include cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, neurologic disease, drug abuse or dependency requiring narcotic replacement therapy, pregnancy, infections with hepatitis C (HCV), hepatitis B (HBV), and tuberculosis (Peeters M: Geographical distribution of HIV-1 group O viruses in Africa. AIDS. 1997).

#### CD4 count monitoring for therapeutic response

Monitoring patients' viral load is critical to identify ART response (WHO 2015). When the viral load analysis is not practical via polymerase chain reaction (PCR), branched chained DNA (bDNA), and nucleic acid sequence-based amplification (NASBA), the CD4 count is used as an indicator of HIV treatment response. During the first year of treatment, increases in CD4 count from 50 - 150 cells/mm<sup>3</sup> with an increased response in the first trimester are considered as a positive response. CD4 count rises steadily ranging from 50 to 100 cells/mm<sup>3</sup> per year until equilibrium is reached in the subsequent years (normal range: 500 cells/mm<sup>3</sup> to 1200 cells/mm<sup>3</sup>). Periodic monitoring of CD4 count is required during and even after the patient achieves normal CD4 count under ART. A number of treatment independent factors like age, viral load, genetic make-up, lifestyle, quality of health care etc., negatively influence the CD4 counts and HIV disease progression. Under such circumstances, a change in ART medication might be required (UNAIDS: Fact sheet 2015).

### III. ADVERSE EFFECTS

#### Major factors for ART non-adherence

##### Adverse Effects of ART

One of the major challenges that patients and physicians face with ART is the incidence of adverse drug reactions (ADR). ADR is defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function". ADR often persuades patients from continuing treatment, thus resulting in suboptimal efficacy. A serious consequence of treatment discontinuation is the emergence of drug resistance, making future therapeutic interventions ineffective.

**The major adverse effects of ART can be grouped into the following categories:**

1. Gastrointestinal: Nausea, diarrhoea, vomiting, taste perversion, constipation, dyspepsia, abdominal pain, hepatotoxicity, and pancreatitis.
2. Central nervous system: Headache, vision problems, dizziness, tinnitus, insomnia, paresthesia, pain/numbness/tingling in extremities, peripheral neuropathy, somnolence, excessive sleep at night, memory problems, loss of olfactory function, and hearing impairment.
3. Haematological: Anaemia, bilirubinemia, increased urate, and blood in the urine.
4. Psychological: Anxiety, confusion, depression, nightmares, elation, and delusions.
5. Metabolic: Abnormal fat distribution (lipodystrophy), anorexia, dyspnoea, fatigue, lethargy, and weight gain.
6. Dermatological: Skin rash, facial discoloration, and pruritus.
7. Musculoskeletal: Body aches and vague chest pain.
8. Miscellaneous: Hypersensitive reactions, oral ulcerations, fever, and irregular menstrual cycles (Khanani RM. AIDS Res Hum retrovirus).

**Drug Abuse**

Continuous drug abuse is an important risk factor in HIV/AIDS patients ART, no adherence, and mortality. In a study conducted on HIV-positive drug addicts in Canada, heroin and cocaine injections were reported to adversely affect adherence to ART. In a separate six-month long longitudinal study, which examined the effect of drug use and abuse on ART among 150 HIV positive patients, it was discovered that acute effects of intoxication negatively influence ART adherence. The major mechanisms by which drug abuse results in ART

Non adherence include drug abuse induced neurocognitive/psychosocial impairment and psychiatric dysfunctions ( Brass AL: Identification of host proteins required for HIV infection through a functional genomic screen. Science. 2008).

**Mental Disorders**

The prevalence of psychiatric disorders is reported to be very high among HIV-infected individuals. In a longitudinal study investigating the mental health, substance abuse, and psychosocial predictors among HIV-positive mothers, the presence of psychiatric disorders, stressful lifestyles, suboptimal living conditions, and parenting stress were associated significantly with ART non adherence. Childhood sexual violence-induced anxiety and depression may also result in ART non adherence. Hazardous drinking is another significant precipitator of anxiety and depression among HIV patients that results in ART non adherence.

**Socioeconomic Status**

Socioeconomic status is strongly associated with HIV-related mortality in the contemporary universal healthcare system because opportunities for patients of lower socioeconomic status to receive ART are meagre. In a study conducted among HIV-positive Cambodian women, 80% of those who discontinued ART were of low socioeconomic status. The estimated risk for low adherence in this population was reported to be five times higher for women than those in a medium or high social position. Poverty-induced stress is an important aspect that has to be addressed in issues regarding ART non adherence. The quality of housing and access to food are the two most important factors that prevent the poverty-ridden population from ART adherence.

**Poor Literacy**

Literacy is another major factor closely associated with ART non adherence with people of lower health literacy experiencing higher illness severity than people with better health literacy. Health literacy has been defined by the WHO as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health”. Many reports suggested that the inability to comprehend medication instructions by illiterate HIV-positive patients is an important factor resulting in failure to follow accurate daily medication therapy.

**Social Stigma**

The stigma of HIV and AIDS is assumed to have a negative influence on ART adherence. Stigma can be defined as an “attribute that is deeply discrediting” imposed by society that reduces someone “from a whole and usual person to a tainted, discounted one”. In a cohort study conducted in five African countries (Lesotho, Malawi, South Africa, Swaziland, and Tanzania) among 1,457 HIV-positive patients over a period of 12 months, individuals perceiving a high HIV stigma reported greater non adherence to ART. Symptom intensity is also high when compared to those who did not experience such a stigma. One study conducted in South Africa reported that internalized stigma is responsible for



4.8% of the variance in cognitive-affective depression leading to ART non adherence. Furthermore, the researchers urge the medical community to introduce social reform efforts to reduce stigma and assist people living with HIV/AIDS in adjusting and adapting. (WHO: Antiretroviral therapy 2015)

#### **IV. REVIEW OF LITERATURE**

The discovery of the human immunodeficiency virus (HIV) as the causative organism of acquired immunodeficiency syndrome (AIDS) and the inability of modern medicine to find a cure for it have placed HIV as the one of the most dreaded pathogens of the 21st century. With millions of people infected with HIV, it was once thought to result in “medical apocalypse”. However, with the advent of antiretroviral therapy (ART), it was now possible to control HIV. Adherence to ART helps to keep the viral load under control and prolong the time of progression to AIDS, resulting in near normal life expectancy. Even with the introduction of ART, a substantial number of patients fail to adhere due to a variety of reasons, including adverse effects, drug abuse, mental disorders, socioeconomic status, literacy, and social stigma. With the availability of so many options for HIV treatment at each stage of the disease progression, physicians can switch between the treatment regimens to avoid and minimize the adverse effects of drugs. Close monitoring, major social reforms, and adequate counselling should also be implemented to circumvent other challenges (de Bethune MP: Antiviral Res. 2010, 85:75–90).

##### **Objectives**

The primary objectives of the review were to systematically collect and review studies on HIV, AIDS, STIs and STDs conducted in India between 2007 and 2019; to assess the quality and reliability of these studies; and to synthesize the research findings under common thematic areas. The secondary objective of the review was to identify relevant recommendations for researchers, policy makers, practitioners, and stakeholders.

##### **Search strategy**

Electronic databases were systematically searched using pre-determined search terms. Internet searches were conducted, and key informants were contacted, in an effort to identify potential studies. The overall search for studies took place between January and May 2021.

##### **Selection criteria**

The inclusion criteria allowed for the following study designs: Randomized Controlled Trials, Cohort Studies, Systematic Reviews, Meta-analyses, Intervention Studies and Evaluations, Case Control Studies, Cross-sectional Studies, Descriptive/Qualitative Studies and Ethnographic Studies. Expert Opinion Studies and Secondary Research Studies were excluded from the review. Studies with participants who were male or female of any age living in India at the time of the study were included in the review. Studies were considered for inclusion if the purpose of the study was to evaluate interventions specific to HIV, AIDS, STIs, or STDs; or if the purpose of the study was to measure outcomes specific to HIV, AIDS, STI or STDs. In addition, studies with the purpose of describing or investigating issues directly related to HIV, AIDS, STIs or STDs in India were also considered for inclusion (Whitcomb JM: Broad nucleoside reverse-transcriptase inhibitor cross-resistance in human immunodeficiency virus type 1 clinical isolates. J Infect Dis. 2003).

##### **Data collection and analysis**

The two authors independently screened the results of the search. The full text of all potentially relevant studies was obtained and studies were independently assessed using pre-determined criteria. The quality of studies included in the review was assessed using validated quality appraisal tools. Common themes were identified via a subgroup analysis (Hughes PJ: A comparative overview).

##### **Main Results**

From the search strategy a total of 2735 citations were identified; 2572 citations were excluded as clearly irrelevant and the full text of 163 studies was reviewed. A total of 23 studies met the inclusion criteria and were assessed for research quality and then analysed for common themes. The majority of studies (n=33) were conducted in National Capital and no studies were conducted in Delhi. Most of the studies were unpublished literature (56%; n=35), and the large majority of studies were cross-sectional in design (92%; n=57). The quality of the studies varied although the majority were rated ‘moderate.’

## Discussion

Limitations of the review were related to publication date, types of study designs, study quality, lack of information, and lack of access to a few electronic databases. The proposed course of action based on this literature review is for a new approach to the HIV national response in India, calling for a 'change to the face of HIV and AIDS.' Under this new approach recommendations include: engagement with the Church as a primary partner in all aspects of strategic planning and implementation; guidance from tradition and culture; more options for women; targeted interventions for married couples; creation of a new national strategy for HIV messages and awareness; prioritization of provincially and community led and driven response; strategies for condom use; positive engagement with PLHIV, and support towards public sector strengthening. Other recommendations are specific to research study type and design as well as suggested indicators for population-based surveys.

## Outline of common themes and key findings

### Tradition, culture, customs, and norms

- Progression from traditional to modern culture
- Socio-cultural norms and practices (*marriage, family and childbearing; violence as a social norm*)
- Interpretations of HIV (*Culture and tradition; conflict between biomedical, Hinduism and traditional beliefs; terminology and language; communication on reproductive and sexual health*)

### Gender

- Gender identities and norms (*men and masculinity; women and femininity*)
- Gender-based violence (*physical violence; sexual violence; counselling and support*)

### Sexuality

- Sexual norms (*traditional and modern meanings of sexuality; sexual identity*)
- Sexual practices (*pre-marital sex and sexual debut; changes in traditional sexual practices; sexual desire; sexual networks, transactional sex; sexual violence and negotiation; types of sex*)

### Sexually Transmitted Infections

- Burden of disease
- Cultural interpretations
- Biomedical treatment and knowledge
- Barriers to STI testing
- STI treatment resistance

### HIV Knowledge

- Modes of transmission
- HIV knowledge in rural settings
- HIV risk perceptions
- Knowledge verses behaviour change

### HIV Vulnerability

- Women
- Men
- Children and young people
- Vulnerability related to poverty and socio-economic decline
- High risk settings and periods of time
- High risk practices

### HIV Prevention

- HIV awareness campaigns (*exposure and sources of information; community led initiatives; responses to the NACO mass media campaign; ABC model*)
- Male condom (*knowledge and use; access and availability; beliefs and experiences*)
- Female condom
- Male circumcision

### HIV Testing

- National and group testing
- Knowledge and attitudes
- Provider initiated counselling and testing
- Barriers to testing (fear of stigma and discrimination; lack of privacy and confidentiality; lack of information and risk perceptions; availability and access of testing sites; testing and treatment)

### Living with HIV and AIDS

- Community responses (*Christian response and socio cultural response; stigma and discrimination*)
- People living with HIV within communities (*knowledge of someone living with HIV; biomedical treatment; traditional medicine and Christian healing; care and support; AIDS related deaths*)

### Leadership

#### Fear as a Responses to HIV

### Public services and government sectors

- Health sector
- Education sector
- Law and justice sector
- Agriculture

### Epidemiology

- National surveillance
  - HIV prevalence in a hospital setting
  - Projection of HIV prevalence
  - Genetics and transmission patterns
- (Greenberg ML: Resistance to enfuvirtide, 2004).

### Analysis

Descriptive and analytical studies that met the literature review inclusion criteria were analysed using grounded theory. A subgroup analysis was performed with the aim of identifying common themes specific to geographical context (study locations and regions), age, gender and areas of interest related to the HIV epidemic in India, including HIV risk, HIV vulnerability, the affects of HIV on particular groups (including people living with HIV), as well as culture, tradition, and religion( RaoPKS;Indian J Sex Transm Dis. 2009).

## V. RESULTS

### Outcome of study

Based on the search strategy, a total of 2735 citations were identified. After reviewing the title and/or abstract of all the citations and removing duplicates, 2572 citations were excluded as clearly irrelevant. The full text was retrieved for the remaining 163 studies. These were reviewed independently by the two investigators. A final number of 23 articles met the inclusion criteria (Arrivillaga M: social determinants of health approach. Rev PanamSalud Publica. 2009, 26:502–10).

## VI. CONCLUSION

Recent advances in HIV treatments have dramatically altered the nature and progression of HIV/AIDS. It can be safely considered as a “chronic” disease, provided the infected patients receive proper ART. Unfortunately, current statistics of the worldwide HIV burden tells another story: one with a steady rate of HIV-related deaths. More people die of complications and the progression of HIV to AIDS than should be when ART is used properly. The major hurdle a physician faces with ART is the incidence of adverse side effects of the treatment, which persuade patients to discontinue the treatment. Poverty, lack of awareness, and the social stigma associated with the infection complicate an already complicated situation. Appropriate changes in treatment regimens and medications can help patients overcome such adverse effects and potential complications inherent to the disease. Additionally, it is highly advisable to provide patients and their immediate family members with appropriate counselling for treatment compliance and psychological support (Willie TC, Hansen NB: Barriers to HIV medication adherence: Behav Med. 2016).

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