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CURRENT SCENARIO OF HIV/AIDS, TREATMENT OPTIONS, AND MAJOR CHALLENGES WITH COMPLIANCE TO ANTIRETROVIRAL THERAPY

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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 has placed HIV as 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 is 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 side 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/or minimize the adverse effects of drugs. Close monitoring, major social reforms, and adequate counselling should also be implemented to circumvent other challenges.

KEYWORDS: hiv, aids, drug adverse effects, hiv/aids, highly active antiretroviral therapy (haart), antiretroviral therapy, clinical managment

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 curse 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.[1] HIV-1 was identified as the causative organism soon after the first official recognition of HIV patients in the USA.[2] HIV-2 was reported first in Africa in 1985 and is markedly different from HIV1.[3] It closely resembles a simian virus that infects macaques in captivity. Simian viruses that naturally infect African primates are suspected to reach humans via multiple cross-species transmissions resulting in the spread of HIV-1 and HIV-2.[2] The global prevalence of HIV has expanded since its discovery and has now spread across the globe despite advances in antiretroviral treatments (ART). The mortality and morbidity rates related to HIV infections remain high in developing countries largely due to food insecurity and malnutrition.[4] Longterm 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.[5]

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 defense mechanisms, 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.[7] HIV infection results in the depletion of CD4 cells in the peripheral blood.[8] Among untreated patients, the depletion continues 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.[9] The following figure represents the timeline of HIV infection from the initial infection to the expression of AIDSdefining symptoms (Figure 2).[10]

HIV subgroups 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.[2] Group N less prevalent, reported only from Cameroon.[11] Group O is accountable for 1% of the total HIV-1 cases and is mainly found Cameroon and Gabon.[12] Group P is the rarest of all and has been identified in Cameroonian pregnant woman in France.[13] It has a prevalence of 0.06% of total HIV infections.[14]

HIV-2

HIV-2 is most commonly reported in West Africa, with Guinea-Bissau and Senegal having the highest incidence. Eight different types of HIV-2 exist, labeled HIV-A to HIV-H. Group A is reported throughout the sub-Saharan region.[15] Group B is reported more commonly in the Ivory Coast.[16] Due to the sporadic nature of the infection and incidence, C to H are categorized as "dead-end" transmissions that produce no subsequent infections.[2]

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 85,000 new HIV infections were reported in 2014, and more than 50% of infections were from the United States of America. About 26,000 AIDS-related deaths were also reported in the same period.[17]

Asia and Pacific

As of 2014, approximately five million individuals were previously infected in Asia and the Pacific, with as many as 340,000 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 240,000 deaths. Patients receiving ART are approximately 36%, with 3.2 million active HIV patients having no access to ART.[17]

Pakistan

In Pakistan, the index case of HIV infections was reported in 1987.[18] As per the annual report of Pakistan National AIDS Control Program, the incidence of HIV has been increasing since first reported. According to UNAIDS, the joint United Nations program on HIV/AIDS, the total number of individuals with an active HIV infection is approximately 94,000. The prevalence rate among adults is between < 0.1% and 0.2%. Currently, there are as many as 26,000 women, age 15 and older, and approximately 2,100 children, up to age 14, currently living with HIV. The total number of AIDS-related deaths in this region was 2,800 in the year 2014.[19]

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.[20] 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).[21] 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. Figure 3 demonstrates the percentage of HIV patients under ART.[22]

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)[23] and nucleoside reverse transcriptase inhibitors (NRTI).[24] 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 noninfectious viral particles.[25] 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.[26] 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.[27] 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.[28] 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.[29] 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.[30]

Latest WHO recommendations for ART A concise form of first, second, and third line treatment options recommended by the World Health Organization (WHO) is given below.[29]

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 favored 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.

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, NVPbased 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.

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 itreatment 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, coinfections with hepatitis C (HCV), hepatitis B (HBV), and tuberculosis (TB).[31]

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 to 150 cells/mm3 with an increased response in the first trimester are considered as a positive response. CD4 count rises steadily ranging from 50 to 100 cells/mm3 per year until equilibrium is reached in the subsequent years (normal range: 500 cells/mm3 to 1200 cells/mm3).[32] 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.

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".[33] 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.[30]

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

1. Gastrointestinal: Nausea, diarrhea, vomiting, taste perversion, constipation, dyspepsia, abdominal pain, hepatotoxicity, and pancreatitis.[34-35] 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.[34] 3. Hematological: Anemia, bilirubinemia, increased urate, and blood in the urine,[35] 4. Psychological: Anxiety, confusion, depression, nightmares, elation, and delusions.[35] 5. Metabolic: Abnormal fat distribution (lipodystrophy), anorexia, dyspnea, fatigue, lethargy, and weight gain.[34-35]

6. Dermatological: Skin rash, facial discoloration, and pruritus.[35] 7. Musculoskeletal: Body aches and vague chest pain.[34] 8. Miscellaneous: Hypersensitive reactions, oral ulcerations, fever, and irregular menstrual cycles.[34]

Drug Abuse

Continuous drug abuse is an important risk factor in HIV/AIDS patients' ART, nonadherence, and mortality.[36] In a study conducted on HIV-positive drug addicts in Canada, heroin and cocaine injections were reported to adversely affect adherence to ART.[37] In a separate sixmonth 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 nonadherence include drug abuse induced neurocognitive/psychosocial impairment and psychiatric dysfunctions.[38]

Mental Disorders

The prevalence of psychiatric disorders is reported to be very high among HIV-infected individuals.[36] 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 nonadherence.[39] Childhood sexual violence-induced anxiety and depression may also result in ART nonadherence.[40] Hazardous drinking is another significant precipitator of anxiety and depression among HIV patients that results in ART nonadherence.[41]

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 meager. 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.[42] Poverty-induced stress is an important aspect that has to be addressed in issues regarding ART nonadherence.[43] The quality of housing and access to food are the two most important factors that prevent the poverty-ridden population from ART adherence.[43]

Poor Literacy

Literacy is another major factor closely associated with ART nonadherence with people of lower health literacy experiencing higher illness severity than people with better health literacy.[44] 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".[45] 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.[46]

Social Stigma

The stigma of HIV and AIDS is assumed to have a negative influence on ART 2016 Bhatti et al. Cureus 8(3): e515. DOI 10.7759/cureus.515 8 of 12 adherence.[47] 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".[48] 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 nonadherence to ART. Symptom intensity is also high when compared to those who did not experience such a stigma.[49] 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 nonadherence. 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.[50]

Clinical management

Diagnosis

The diagnosis of HIV-1 infection is based on the detection of specific antibodies, antigens, or both, and many commercial kits are available. Serological tests are generally used for screening. A major advance has been the availability of rapid HIV-1 antibody tests. These assays are easy to do and provide results in as little as 20 minutes,[51] enabling specimen collection and proper diagnosis at the same visit. Rapid tests are important tools for surveillance, screening, and diagnosis, and can be reliably done on plasma, serum, whole blood, or saliva by health-care providers with little laboratory expertise. The two limitations of these serological tests are detection of infection during primary infection when antibodies are absent, and in infants younger than 18 months who might bear maternal HIV-1 antibodies. In these instances direct virus detection is the only option (eg, quantification of viral RNA [standard] or p24 antigen in heat denatured serum [less expensive]).

For staging purposes, measurement of CD4+ cells and viraemia is required. Plasma viral load is widely used to monitor therapeutic success on antiretroviral treatment. Several commercially available tests provide sensitive quantification of plasma HIV-1 RNA copies. The newer versions of the Amplicor and Quantiplex (Roche, Indianapolis, IN, USA, and Bayer Diagnostics, Walpole, MA, USA, respectively) assays have overcome initial suboptimum performance for non-B subtypes.102 While the viral load determines the rate of destruction of the immune system, the number of CD4+ cells reveals the degree of immunodeficiency and is, therefore, used to assess the stage of infection. CD4+ cell counts together with clinical manifestations (eg, occurrence of opportunistic infections) are key criteria for HIV-1 disease classification. Flow cytometry analysis is the standard method for CD4+ cells quantification.

Standard methods for quantifying viral load and CD4+ cell counts need advanced laboratory infrastructures, and assays require a specimen to be tested within a short time of collection. These requirements pose challenges for resource-constrained settings. The use of dried blood spot specimen has resolved some of the difficulties associated with transportation of samples needed for virological assessments.[53] Measurement of reverse transcriptase activity in plasma samples, simplification of gene amplification methods (eg, Taqman technology), and paper-strip quantification (dipstick assays) might provide cost-effective alternatives for the future.[54–56] Similarly microcapilliary flow-based systems, CD4+ chips, or total white counts (panleucocyte gating) provide alternatives for establishment of the level of immunodeficiency in resource-limited settings.[57–60]

Drug treatment

Antiretroviral compounds

Antiretroviral treatment is the best option for longlasting viral suppression and, subsequently, for reduction of morbidity and mortality. However, current drugs do not eradicate HIV-1 infection and lifelong treatment might be needed. 20 of the 21 antiretroviral dr+ugs currently approved by the US Food and Drug Administration target the viral reverse transcriptase or protease (table 2). Eight nucleoside/ nucleotide analogues and three non-nucleoside reverse transcriptase inhibitors inhibit viral replication after cell entry but before integration. Fixed-dose combination tablets simplify treatment regimens by reducing the daily pill burden, and drugs with long half-lives allow once or twice daily dosing. Eight protease inhibitors prevent the maturation of virions resulting in production of non-infectious particles. The recently approved darunavir (June, 2006) is the first of its class that retains activity against viruses with reduced susceptibility to protease inhibitors. Enfuvirtide targets a gp41 region of the viral envelope and stops the fusion process before the cell is infected. This drug needs to be injected twice daily and its use is reserved for treatment of heavily drug-experienced patients since it can help overcome existing drug resistance.[61,62] Development of new antiretrovirals focuses on molecules that target entry, reverse transcription, integration, or maturation. Compounds that have been designed to inhibit resistant viruses are urgently needed since many patients treated during the past decades harbour viral strains with reduced susceptibilities to many if not all available drugs.

The goal of antiretroviral treatment is to decrease the morbidity and mortality that is generally associated with HIV-1 infection. A combination of three or more active drugs is needed to achieve this aim in most patients. Effective treatment returns to near normal the turnover rates of both CD4+ and CD8+ T-cell populations.[63] Potent but well tolerated drugs with long half-lives and simplified regimens improve the options for first-line and secondline chemotherapeutic interventions.

Combination antiretroviral treatment

High rate of viral replication, low fidelity of reverse transcription, and the ability to recombine are the viral characteristics that lead to the diversity of HIV-1 species (quasispecies) in chronically infected individuals. This high genetic variability provided the rationale for highly active antiretroviral treatments (HAART). By combination of several potent antiretroviral agents, viral replication is suppressed to such low levels that emergence of drug resistant HIV-1 variants was, if not prevented, at least delayed. By doing so, CD4+ T-lymphocyte numbers increase, leading to a degree of immune reconstitution that is sufficient to reverse clinically apparent immunodeficiency. Widespread introduction of HAART in industrialised countries resulted in a striking decrease in morbidity and mortality, putting forward the hope that HIV-1 infection can be transformed into a treatable chronic disease.[64-66]

A set of criteria composed of plasma viraemia concentration, absolute or relative CD4+ cell counts, and

clinical manifestations, is used to recommend initiation of HAART. The benefits of treatment clearly outweigh the potential side-effects in patients with clinical signs of immunodeficiency (eg, AIDS defining illnesses) or with CD4+ numbers less than 200 per μL (recommendation of US Department of Health and Human Services, October, 2005). However, the best time point to begin treatment remains controversial in asymptomatic patients with modest depletion of CD4+ T cells (eg, more than 350 per μL) and modest levels of viraemia (eg, less than 100 000 copies per mL).[67] Studies with clinical endpoints supporting the validity of early versus late interventions in asymptomatic patients are difficult to do and insufficient clinical data are currently available. Early depletion of gut CD4+ T lymphocytes,[68] increasing viral diversity, and the poor regenerative abilities of key populations of the immune system provide arguments for beginning treatment as early as possible. The wide application of this principle is restricted by long-term drug toxicities that lead to reduction of quality of life, and by treatment costs. Toxicities (eg, renal, hepato, mitochondrial), metabolic changes (eg, lipodystrophy, diabetes mellitus), and immune reconstitution disease are some of the long-term problems that complicate decade-long HAART.[69-72]

One strategy addressing life-long daily compliance to HAART has been structured treatment interruptions. The rationale for this approach was based on the premise that the body's own immune system could keep the virus in check if exposed to a very modest level of viral replication. If successful, this strategy could limit drug toxicity and reduce treatment costs.[73] Although preliminary findings for this strategy were mixed in terms of benefits,[74-76] the recent early closure of the SMART trial was based on increased morbidity and mortality in the treatment interruption arm.[77] Thus, in the absence of clinical benefits, most investigators strongly discourage treatment interruptions except as needed to address treatment intolerance.

HAART in resource-constrained settings

The transformation of AIDS into a chronic disease in industrialised countries has yet to be realised in resource-constrained settings. Access to HAART is an absolute humanitarian necessity to avert mortality in people who are central to the future survival of their countries.[78] Despite restricted health infrastructures and diverse co-morbidities in these regions, remarkable therapeutic success rates have been shown, with adherence rates at least comparable with those reported in industrialised countries.[79-82] WHO and UNAIDS treatment guidelines focusing on resource-limited settings suggest use of standard first-line regimen followed by a set of more expensive second-line options.[83] and proposes the use of standardised decision-making steps (eg, when to start, to substitute for side-effects, to switch for virological failure).[83,84] In many countries, treatment options are limited not only by the costs of HAART but also by restrictive licensing policies, and current estimates suggest that 80% of people infected with HIV-1 with a clinical need for treatment do not yet have access to antiretroviral drugs.1 Thus, efforts and strategies to further scale up treatment access are crucial,[85-88] since antiretroviral treatment is also an effective intervention for prevention.[89]

Drug resistance

Emergence of drug resistance is the most common reason for treatment failure. Insufficient compliance, drug side-effects, or drug-drug interactions can lead to suboptimum drug concentrations, resulting in viral rebound. Viral resistance has been described to every antiretroviral drug and therefore poses a serious clinical as well as public-health problem.[90] HIV-1 subtypes differ in the sequence of mutations leading to drug resistance, and some naturally occurring polymorphisms might actually modulate resistance.[91,92] Drug-resistant HIV-1 is transmissible and can be detected in up to 20% of newly infected individuals in countries with broad access to antiretrovirals.34 The prevalence of drug resistance in the untreated population remains low in regions with poor access to treatment.[93]

Short-term antiretroviral-based interventions are effective in prevention of mother-to-child transmission. However, these interventions could result in drug resistant viral variants in the mother, baby, or both.[94] Around half the women who received one dose of nevirapine to prevent mother-to-child transmission harbour viruses resistant to non-nucleoside reverse transcriptase inhibitors (NNRTI).[95,96] These resistant viruses replicate efficiently and canbe transmitted by breast milk,[97] and minor resistant populations present long after the intervention can possibly decrease the effectiveness of subsequent NNRTI-based treatment regimens.[98] The combination of short-course zidovudine, lamivudine, and nevirapine prevents peripartum transmission while reducing the risk of nevirapine resistant viruses.[99]

CONCLUSIONS

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 counseling for treatment compliance and psychological support.

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