Review Article

A review of some Antiretroviral therapies used in Management of HIV/AIDS in Ghana

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Abstract

HIV is a RNA retrovirus that causes progressive weakening of the host's immune system increasing susceptibility to opportunistic infections. Antiretroviral drugs are currently used to manage the infection. This paper reviews the benefits and the toxicity associated with ARTs currently used in Ghana. Google search, PUBMED and Google scholar were used to gather information from different books, websites and peer-reviewed journal articles. ARTs significantly improved the quality of life of people living with HIV/AIDS by increasing the CD4 count and reducing the viral load. ARTs have short and long term side effects which may be life threatening. Toxicity may vary from drug to drug and from one drug class to the other. We conclude that it is important to select a regimen that is not only effective but also safe. This requires consideration of not only the toxicity potential of an ARV regimen but also an individual patient's underlying conditions, concomitant medications and history of drug intolerance.

Introduction

The Human Immunodeficiency Virus (HIV) is a lentiretrovirus with a complex genome. It causes progressive weakening of the host's immune system increasing susceptibility to opportunistic infections. The complication of HIV infection is Acquired immunodeficiency syndrome (AIDS) and death if unmanaged. Two types of the virus have been identified; HIV-1 which is the primary cause of AIDS world wide and HIV-2, found mostly in West Africa. It presently has no cure [1, 2].

In 2009, HIV epidemic affects about [33.3] million people with most cases (about 30 million) in developing countries especially in sub-Saharan Africa (SSA). In 2010, 9 million Cases of HIV infection required antiretroviral therapy but only over 6 million were able to access treatment in SSA. [3, 4]

ART used in HIV infection include Fusion inhibitors (FI), Protease inhibitors (PIs) Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTI) and Integrase inhibitors [6]

Currently, the World health organization (WHO) recommends multiple-drug combination therapy for treatment of HIV disease known as highly active retroviral therapy (HAART)[7]. It includes a combination of at least three retroviral drugs into a fixed dose.

HAART has improved the quality of life of people living with HIV infection and has also significantly reduced mortality, morbidity from HIV co-infections and viral transmission rates. [1,5,7,8].

Despite the laudable achievements of HAART in combating HIV infection, like other drugs, they posses toxicities which could be life threatening.

This paper attempts to look into some common antiretroviral drugs in use (with emphasis on those available in Ghana) as approved by the WHO, their mechanisms of action, clinical use (benefits) and potential side effects.

The HIV infection

The first case of HIV infection in Ghana was recorded in 1986. HIV -1 infection accounts for 95.9% of infection, HIV -2 and co-infection of HIV 1 and 2

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accounting for 1.5% and 2.6% respectively [9]
HIV is transmitted through contact with infected body fluids (e.g. semen and whole blood), infected sharp objects (as used in circumcision and scarification), and mother - child transmission (15%). Sexual intercourse is the most common primary route of infection (about 75 - 80%). Women are however at higher risk of infection because of the vagina serves as the reservoir for infected semen. HIV carries the most serious social stigma among the sexually transmitted viral infections. [9,10]

Numerous co-infections have been associated with HIV infection. Hepatitis B and C co-infection with HIV is thought to be due to similar routes of transmission of the infections. It is associated with more rapid progression of viral hepatitis-related liver disease (e.g. cirrhosis, hepatocellular carcinoma, and fatal hepatic failure) [7,8]

HIV infection significantly increases the risk of active pulmonary tuberculosis by immunosupression 2. Other co-infections include opportunistic viral, bacterial, parasitic and fungal infections, HIV-associated nephropathy, cardiovascular diseases (which account for 10% of HIV related mortality) and diabetes mellitus. [7]

The HIV replication cycle

The HIV virus has a short replication cycle of about 1.5days. The HIV virus enters the host cells by attaching to the cell membrane's cluster of differentiation antigen 4 cell (CD4) receptor by viral membrane glycoprotein 120 (gp 120). Attachment is aided by CCR5 co-receptor of T-lymphocytes and CXCR4 co-receptors on macrophages. Upon penetration and uncoating, there is rapid replication of the virus involving the use of a reverse transcriptase to make a double stranded viral DNA that is incorporated into the host cell's DNA (in the nucleus) using the enzyme integrase. The host cell transcribes viral mRNA which is translated into early and late phase proteins, makes more copies of viral RNA which are assembled in the cytoplasm into virions. The virons mature by cleaving large polyproteins into smaller proteins by viral proteases and are surrounded by an envelope derived from the host cell membrane. [10, 11]

HIV establishes latency in the nucleus of infected cells, usually not causing lysis, churning out millions of infective viral particles that infect other host cells. Its rapid replication cycle and mutation rate (due to lack of proofreading enzymes, leading to high genetic variability) make it very difficult to develop an effective vaccine 11. Our present hope of HIV treatment is ART.

Classification of Antiretroviral therapy (ART)
The stages of the replication cycle of HIV are potential points for viral inhibition and hence form basis for ART classification. [6, 12]

Fusion or Entry Inhibitors:

They relatively new class of antiretroviral agents first approved in 2003 for treating HIV infection. They prevent the entry of the HIV into human immune cells. Enfuvirtide is the first representative. It binds to the gp41 subunit of the viral envelope protein and prevents the conformational change required for fusion of viral and host's cell membrane. [12]

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIS)

They were first approved in 1987. Zidovudine was the first agent to be developed in this class. Others include abacavir,didanosine, stavudine, lamivudine, tenofovir. They are phosphorylated by intracytoplasmically by cellular enzymes to active forms which competitive inhibit HIV reverse transcriptase (see fig 1 above). They could also be incorporated into the growing viral DNA chain and cause chain termination. [6,8,12,13]

ZIDOVUDINE (3'-azido-3'-deoxythymidine, AZT):
Available in Ghana as Combivir (with Lamivudine) administered orally as one tablet twice daily 9. It is the first known antiretroviral drug and the commonest in SSA 8. It is a thymidine analogue administered at an adult dose of 300mg. Following oral administration, Zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism hence dosage needs to be adjusted in hepatic failure.

Intracellularly, Zidovudine is phosphorylated to its active 5'-triphosphate metabolite, Zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. AZT reduces viral transmission rates (especially to women with HIV RNA <1,000 copies/mL) when administered early in pregnancy to prevent mother-child transmission and prophylaxis

for high risk health workers etc.
Toxic effects include severe anaemia, gastrointestinal disturbance (e.g. diarrhea, vomiting and flatulence), lactic acidosis, lipodystrophy, neutropenia, gonadotoxicity. [1,3,12,14]

LAMIVUDINE (2',3'-dideoxy, 3'-thiacytidine, 3TC):
It was originally used to treat hepatitis B infection. It is administered at an adult dose of 150mg, twice daily. Following oral administration, Lamivudine is rapidly absorbed and extensively distributed. It is mostly excreted in urine unchanged. It possesses fewer toxic effects. However rare cases of neutropenia have been documented.[3,12,15]

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIS)
They were approved for use in 1996. They bind directly to HIV -1 reverse transcriptase resulting in blockage of RNA and DNA-dependent DNA polymerase. The binding site is distinct from that of NRTIs. They require no phosphorylation and are not incorporated into the growing viral DNA chain. Delavirdine, efavirez (used in treatment of HIV/TB co-infection in Ghana) 2, nevirapine, rilpivirine are examples.

Nevirapine
It was approved for use in 1996. It is effective against HIV-1 but not HIV-2 infections. This is because the allosteric site of the virus has a different structure that nevirapine (and other NNRTIs) cannot bind to. It is administered orally at an adult dose of 200 mg. Metabolized is by the liver's CYP450 system and excreted in feces (10%) and also urine (80%).

It is endorsed by the WHO as prophylaxis in many developing world settings (including Ghana) as a cost-effective way of reducing mother-to-child transmission.

Life threatening hepatotoxicity is the major toxic effect of this drug. However unlike other hepatotoxic ARTs, nevirapine's toxicity increases with a higher patient CD4 count. Others include rashes and Steven Johnson's syndrome [7,12,15]

PROTEASE INHIBITORS (PIs)
Approved for use in 1995; they inhibit the maturation of the newly formed virus by inhibiting the protease responsible for cleaving precursor molecules (polyproteins) into mature structural proteins, giving rise to immature and noninfectious viral particles. Examples include indinavir, saquinavir, rotinavir. [7, 12]

Integrase Inhibitors Or Intergrase Standard Transfer Inhibitors (INSTIS):
They are the newest class of drugs and were approved for HIV treatment in 2007. They interfere with the integrase enzyme, which HIV needs to insert its genetic material into human cells. Zintevir is an example. [6]

CCR5 antagonists e.g. Maraviroc, maturation inhibitors e.g. alpha interferon are also in use [7].
Currently, WHO suggests the use of ART for all people living with HIV (PLHIV) with a CD4 count of =350 cells/mm3 and for those with WHO clinical stage 3 or 4 (if CD4 testing is not available). [7]

The cost of ARTs in Ghana
Initially ARTs cost $US 10,000 - $15,000 per person per year. This was too expensive for most patients in the developing countries, including sub-Saharan Africa - the worst hit area with the HIV epidemic 1. The availability of cheap ARTs -was made possible by the UNITAID's focused programmes (in conjunction with pharmaceutical companies) and subsidy by government. [8,9,14,16]

In Ghana, the subsidized ARTs are Combivir (a combination of Zidovudine and Lamivudine), Viracept (Nelfinavir) and Nevirapine (free for pregnant women). Combivir and Viracept cost $US 124-200 and $282 respectivley. [8,9]

The most widely used drug combination (d4T+3TC+NVP) is available for $US 52-64 per person per year. However, WHO recommends that countries phase out its use due its severe side effects usually attributed to stavudine (d4T) but it is still a widely used ART in children. [8,14]

Highly active antiretroviral therapy (HAART)
They were introduced in 1996. It involves three or four antiretroviral drugs combined into a single dose containing two NRTI plus one active drug from other ART classes usually NNRTI, PI (usually boosted with ritonivir, RTV), INSTI or a CCR5 antagonist. The preferred HAART in Ghana includes a

combination of AZT+3TC+NVP as first line regimen [8.13.]

Materials and Methods

Google search, PUBMED and Google scholar were used to gather information from different books, websites and peer-reviewed journal articles.

Results

ART significantly reduced morbidity and mortality rates (by 30 -80%), reduced viral load in most subjects, increased CD4 count, reduced transmission rates [7,8,24,25] (table I).

Common toxicities were lipodystrophy, lactic acidosis, hepatotoxicity, hematotoxicity and osteotoxicity [23-31] (table II).

Table 1: Effects of ART on HIV infection

Evaluated parameter	Effect of ART	Comments
Morbidity and Mortality rates	Avertion of 2.5million deaths globally (since 1995), 1.8million, from sub-Saharan Africa [8]. Improved survival, delayed progression and reduced AIDS-related complications in patients with advanced HIV disease. Preserved renal function in patients with HIV-associated neuropathy [17], may attenuate liver disease progression in persons coinfected with HBV and/or HCV, reduced cardiovascular risk when (ART is started early)[7,19], reduce the risk of both HIV related, AIDS and non-AIDS-defining malignancies [7]. decline in the incidence of HIV associated dementia from 6.49 per 1,000 person-years (before 1997) to 0.66 per 1,000 person-years (2003−2006) [7]	The presence of chronic viral hepatitis increases the risk of ARV-induced liver injury; however, majority of coinfected persons do not develop clinically significant liver injury [7,18] Some studies showed higher cardiovascular risk [20,21] especially with treatment interruption [22].
Viral transmission rate	Significant reduction in perinatal transmission (20%–30% to <2% in the United states). Statistically significant decline in HIV prevalence among pregnant women attending antenatal clinics in Ghana (by 39% from 2001 – 2010). Decreased rate of HIV transmission among serodiscordant heterosexual couples [8].	
Viral load	Reduction in viral failure rates. Optimal viral suppression was observed as <20–75 copies/mL. Viral load <200 copies/mL was also observed in some studies, hence marked as low-level positive viral load. viral suppression was generally achieved in 12–24 weeks [7]	When initial suppression is not achieved or is lost, rapidly changing to a new regimen with at least two active drugs is required [7].
CD4 count	Increased by 50–150 cells/mm3 of blood (in the 1st 3 months of early commencement of ART) in ART naïve patients [7]	The CD4 cell count response to ART varies widely, but a poor CD4 response is rarely an indication for modifying a virologically suppressive ARV regimen. CD4 Percentage estimation is a better indicator. [7]

Table II: Toxicity of ARTs

Toxic effect	Implicated ART	Comments
GI SYMPTOMS	Most ART groups [22]	Nausea, vomiting, diarrhea are common. Symptoms may be transient or persist throughout the use of therapy
CNS TOXICITY [3,7,22] Nightmares Peripheral neuropathy Retinoid toxicity Fatigue	 NVP d4T PI Most ARTs	 Usual side effect of NVP was mild as rash. Severe rash (Steven - Johnson syndrome) however should cause discontinuation of NVP.
METABOLIC [3,22] lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia.	 Most NRTIs Usually with d4T Most ARTs Usually with PIs	Lactic acidosis may mimic GI symptoms and hence should be suspected in patients experiencing GI symptoms. 10-20% of patients experienced hyperlactemia PIs usually cause elevation of liver enzymes. NVP induced hepatotoxicity was observed in 8.9% of patients.
LIPODYSTROPHY [22] fat maldistribution, Hyperlipidemia, insulin resistance	Most ARTs	50% of patients experience at least one physical abnormality of lipodystrophy during one year of ART administration
HEMATOTOXICITY [3,7, 22] Anemia Neutropenia Bleeding episodes in hemophilia	 AZT 3TC	
OSTEOTOXICITY [22] Osteoporosis and osteronecrosis	 Most PIs, NVP	

Discussion

The aim of this research was to review ARTs used in treatment of HIV infection, some of their benefits and toxic effects were also explored.

The CD4 count is the strongest predictor of subsequent disease progression 24 and HIV transmission 7,8. Patients with CD4 count <200 cells/mm3 are at higher risk of opportunistic diseases, non-AIDS morbidity, and death 7. In clinical trials, lamivudine in combination with zidovudine (known as combivir in Ghana) has been shown to reduce HIV-1 viral load and increase CD4 cell count in a synergistic manner 1,3. This increase in CD4 count in HIV infected patients who begin ART was attributed to reduced rate of viral replication leading to reduced viral load and improved immunological response [1,3,7]. Early onset administration of ART has also shown to improve patient outcome than late onset [7,8,25].

A reduction in viral load was also observed on administration of ART to ART naïve patients (appendix 1). Reduced viremia positively correlates with better clinical outcome and lower viral transmission rates [7,25]. Latent HIIV infection is said to remain because the pool of infected CD4 T-cells established during the earliest stages of acute HIV infection which persists with a long half-life, despite prolonged suppression of plasma viremia by ARTs. [7, 26]

Predictors of reduced viremia include high potency of ART, excellent adherence to treatment regimen, low baseline viremia, higher baseline CD4 count (>200 cells/mm3). This is why the WHO advocates for early commencement of ART 7. Slow reduction in viremia despite ART commencement, suggests the presence of transmitted drug-resistant virus. This is observed in up 16% of ART naïve patients [7,24].

ART toxicity may be class-specific or peculiar to an ARV (appendix 2)

Lactic acidosis caused by NRTIs results from inhibition of DNA polymerase causing diminished mito-

chondrial function. Pyruvate is converted to lactate. Impaired oxidation leads to a decrease in fatty acid oxidation causing them to accumulate; stimulating lipogenesis. The excess triglycerides accumulate in the liver, causing hepatic steatosis. Other symptoms include hyperlactemia, fatigue, dyspnea, tachypnea, nausea and weight loss. [23]

Lipodystrophy was first observed in HIV/AIDS patient in1998 23. Patient's age and advanced HIV disease are presently been considered as risk factors. [23,27]

Dyslipidemia to levels associated with increased risk of cardiovascular disease occurs in about 70% of HIV-1 infected patients receiving antiretroviral therapy. It also increases the risk of cardiovascular diseases and insulin resistance leading to hyperglycemia usually without frank diabetes mellitus. [23,28]

Hepatotoxicity associated with most of the antiretroviral agents is possibly due to interaction with liver enzymes during metabolism 23. Most studies implicated PIs as more usual causes of hepatotoxicity. The rate of severe ART induced hepatotoxicity among patients with hepatitis C infection is higher than those without the infection [7,23,29].

Antiretroviral associated lactic acidosis, phosphate compensation for anion gap30, inhibition of new bone formation by stimulating osteoclast activity or inhibiting osteoblast activity 31, metabolizing by cytochrome P450 enzymes, the oxygenase that activates vitamin D 23 have been suggested as causes of ART induced osteoporosis

Hematotoxicity of ARTs especially with the use of NRTIs like AZT can cause life threatening anemia, possibly due to bone marrow suppression.[2]

Conclusion

Although the therapeutic goals of ART include achieving and maintaining viral suppression and improving patients' immune function, it is important to select a regimen that not is only effective but also is safe. This requires consideration of not only the toxicity potential of an ARV regimen but also an individual patient's underlying conditions (e.g. successful treatment of hepatitis C in dually infected patients before the introduction of PI-containing antiretroviral therapy), concomitant medications, and history of drug intolerance.

Pretreatment genotypic resistance testing is also advised as guide to selecting the most beneficial initial ARV regimen for a patient.

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