Abstract
Human immunodeficiency virus (HIV) infection is a global pandemic, with cases reported virtually from every country. HIV/AIDS being one of the world’s recent most devastating diseases, nearly 25 million people have died worldwide due to HIV infection since June 1981, when it was first diagnosed. According to the WHO, 33 million people worldwide are living with HIV. To provide access to highly active antiretroviral therapy (HAART), to the whole HIV suffering population remains a major goal to accomplish. Several studies have suggested that HAART improves renal function and prognosis for patients with HIV. Many individuals diagnosed are already with advanced renal disease and then due to lack of renal replacement therapies the mortality rate rises. HIV associated nephropathy (HIVAN) outcomes correlate with the clinical stage of the disease suggesting that early detection improves patient survival. On the other hand, with significant reductions in mortality and risk of progression to AIDS in the era of HAART, complications of long standing HIV infection and treatment should be dwelt with extreme importance. Most common nephrotoxic effects of antiretroviral include crystal-induced obstruction secondary to the use of protease inhibitors (indinavir and atanavir) and proximal tubule damage related to nucleoside reverse transcriptase inhibitors tenofovir. Acute kidney injury (AKI) can occur following tenofovir induced tubular dysfunction or because of mitochondrial dysfunction and lactic acidosis induced by nucleoside reverse transcriptase inhibitors. However looking to the benefits of HAART, fear of nephrotoxic effects can never be a valid reason for physicians to withhold antiretroviral therapy. Hence, identification of patients with pre-existing chronic kidney disease, who are at increased risk of renal damage, enables appropriate dose modifications, close monitoring and avoiding potential nephrotoxic drugs. Putting into practice some of the guidelines can further help save the renal complications.

Key words: HIV, HAART, Kidney, Nephrotoxic

Introduction
Kidney proves to be the major excretory pathway for many drugs and their metabolites. Proximal tubule plays an important role due to its high rate of blood flow and the high level of toxins it has to process and hence this part of the kidney is always vulnerable to develop drug related damage. With the introduction of HAART, which has led to a dramatic decline in the mortality and morbidity of HIV infection, varieties of adverse renal effects have come up. Furthermore, improved survival among patients with HIV is anticipated to result in an increase in the risk of chronic HAART-associated metabolic complications, such as diabetes and dyslipidemia, which in turn can contribute to vascular damage and decreased renal function. Understanding the pathogenesis of HIV/AIDS, the HIV replication cycle and the mechanisms of HAART-related kidney disease is essential to adapt to future preventive measures such as dose adjustments, avoiding nephrotoxic drugs in patients at risk of developing kidney disease or having underlying renal diseases.

Anti-retroviral for the treatment of HIV/AIDS
Anti-retroviral drugs acting against the HIV are divided into 4 classes, which have received FDA approval: protease inhibitors (PIs), fusion inhibitors, non-nucleoside analog reverse transcriptase inhibitors (NNRTIs) and nucleoside/nucleotide analog reverse transcriptase inhibitors (NRTIs) (Table I). Of the 25 ARVs that have been approved, 3 are no longer being manufactured, either because of the development of improved formulations (i.e., amprenavir* replaced by fosamprenavir*) or because of limited use (i.e., delavirdine and zalcitabine). Currently, there are 22 antiretroviral agents available for clinical use. Several others are in various stages of basic and clinical development. As of February 2009, 17 of these have an approved pediatric treatment indication (noted with * below), and 16 are available as a pediatric formulation or capsule size.

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These agents are the CCR5 antagonist (maraviroc) and fusion inhibitor (enfuvirtide*), which prevent viral entry; the nucleoside/nucleotide reverse transcriptase inhibitors (abacavir*, didanosine*, emtricitabine*, lamivudine*, stavudine*, tenofovir, zalcitabine, and zidovudine*) and non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz*, etravirine, and nevirapine*), which act at the early stage of replication, prior to viral integration into the host genome; one inhibitor of viral genome integration into host genetic material (raltegravir); and the protease inhibitors (amprenavir*, atazanavir*, darunavir*, fosamprenavir*, indinavir, lopinavir/ritonavir*, nelfinavir*, ritonavir*, saquinavir, and tipranavir*), which exert their effects when the integrated HIV genome is subsequently expressed, by interfering with cleavage of HIV proteins by the viral protease. New classes of antiretroviral agents, such as maturation inhibitors, are currently under investigation. Understanding how these drugs work, what their potential adverse effects are, and how they interact with each other as well as with other concomitantly administered drugs, play a critical role to achieve successful treatment outcome (1).

Table I. Anti-retroviral drugs acting against the HIV.

<table>
<thead>
<tr>
<th>DRUG GROUP</th>
<th>NAME OF DRUG</th>
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<tbody>
<tr>
<td>Protease Inhibitor (PIs)</td>
<td>Atazanavir (ATZ)</td>
</tr>
<tr>
<td></td>
<td>Darunavir (DRV)</td>
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<tr>
<td></td>
<td>Fosamprenavir (FPV)</td>
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<td></td>
<td>Indinavir (IDV)</td>
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<td>Lopinavir (LPV)</td>
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<td></td>
<td>Nelfinavir (NFV)</td>
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<td>Ritonavir (RTV)</td>
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<td>Saquinavir (SQV)</td>
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<td></td>
<td>Tipranavir (TPV)</td>
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<tr>
<td>Fusion/ Entry inhibitors</td>
<td>gp41 {Enfuvirtide (T20) }</td>
</tr>
<tr>
<td></td>
<td>CCR5 (Maraviroc, Vicriviroc, PRO 140)</td>
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<td></td>
<td>CD4 (Ibalizumab)</td>
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<td>Reverse transcriptase inhibitors</td>
<td>Non-Nucleoside (NNRTI)</td>
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<tr>
<td></td>
<td>Efavirenz</td>
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<td></td>
<td>Nevirapine</td>
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<td></td>
<td>Diarylpyrimidines</td>
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<td></td>
<td>(Etravirine, Rilpivirine)</td>
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<td></td>
<td>Loviride</td>
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<td></td>
<td>Delavirdine</td>
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<td>Nucleoside and Nucleotide (NRTI)</td>
<td>Nucleoside analogues/NRTIs</td>
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<tr>
<td></td>
<td>Abacavir (ABC)</td>
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<tr>
<td></td>
<td>Etricitabine (FTC)</td>
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<tr>
<td></td>
<td>Didanosine (ddI)</td>
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<td></td>
<td>Lamivudine (3TC)</td>
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<td></td>
<td>Zidovudine (AZT)</td>
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<td></td>
<td>Apricitabine</td>
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<td>Stampidine</td>
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<td>Elvucitabine</td>
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<td>Racivir</td>
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<td>Amdoxovir</td>
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<td></td>
<td>Slavudine (d4T)</td>
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<td></td>
<td>Zalcitabine (ddC)</td>
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<tr>
<td>Combined formulations:</td>
<td>Tenofovir</td>
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<tr>
<td></td>
<td>Adefovir</td>
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Protease inhibitors

HIV-1 protease is responsible for the cleavage of the large viral precursor polypeptide chains into smaller, functional proteins, thus allowing maturation of the HIV viron (2). There are 10 PIs currently approved for clinical use.

Crystal nephropathy- 30 cases of atazanavir-associated nephrolithiasis were recorded in the adverse Event Reporting System database (3). Few case reports have been published of atazanavir associated chronic kidney disease (4).

Delavirdine, and efavirenz. For the treatment of HIV at the present time: nevirapine, and delavirdine and blocks the formation of the 6-helix bundle necessary for HIV-1 infection. It is not active against HIV-2. Possible side effects were found in some case report showing Membranoproliferative glomerulonephritis. But studies still to be conducted further for more precise proofing.

Fusion Inhibitors

Enfuvirtide (also known as T-20) is the first, and thus far the only, fusion inhibitor to be approved by the FDA. It is a linear 36- amino acid peptide homologous to a segment of the HR2 region of gp41. It binds to the HR1 region of gp41 and blocks the formation of the 6-helix bundle necessary for fusion. Enfuvirtide is indicated for the treatment of HIV-1 infection. It is not active against HIV-2. Possible side effects were observed (4).

Renal involvement- several cases of AK, some requiring dialysis were reported in association with full-dose (400mg twice daily) ritonavir therapy. But the etiology of renal damage is unknown (6). Long term therapy with indinavir could cause CKD and renal atrophy associated with severe hypertension.(7, 8) Protease inhibitors have been shown to be contributing to a 10mmHg rise in blood pressure and are involved in development of diabetic nephropathy(8, 9, 10).

Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors bind directly and noncompetitively to the enzyme reverse transcriptase (11, 12). Although these drugs differ structurally from each other, they all share the same mechanism of action, binding to a site on the reverse transcriptase enzyme that is distinct from the substrate (dNTP) binding site and blocking DNA polymerase activity by causing a conformational change and disrupting the catalytic site of the enzyme (13). Unlike nucleoside analogs, NNRTIs do not require phosphorylation to become active and are not incorporated into viral DNA. They also have no activity against HIV-2 (14). There are 3 NNRTIs approved for the treatment of HIV at the present time: nevirapine, delavirdine, and efavirenz.

As small number of cases of crystalluria or obstructive uropathy associated with the use of NNRTI agent efavirenz are reported (15). Nucleoside/nucleotide analog reverse transcriptase inhibitors

Nucleoside analog reverse transcriptase inhibitors are the first antiretroviral drugs to be approved for the treatment of HIV. The NRTIs are potent inhibitors of the HIV reverse transcriptase (RT) enzyme, which is responsible for the reverse transcription of viral RNA into DNA; this process occurs prior to integration of viral DNA into the chromosomes of the host cell. The antiviral activity of NRTIs depends upon intracellular serial phosphorylation by host cellular kinases to the active triphosphate drug (16). The phosphorylated drug competitively inhibits viral reverse transcriptase and, following incorporation of the drug into the growing DNA chain, terminates further elongation of viral DNA. Because these drugs act at a pre-integration step in the viral life cycle, they have little to no effect on chronically infected cells, in which proviral DNA has already been integrated into cellular chromosomes.

Like the NRTIs, nucleotide reverse transcriptase inhibitors (NRTIs) also competitively inhibit the viral reverse transcriptase, but because the nucleotide drugs already possess a phosphate molecule (the NRTIs do not), the nucleotide drugs bypass the rate-limiting initial phosphorylation step required for activation of NRTIs. Although resistance to these agents eventually develops during the course of long-term single-drug therapy, combination therapy with these drugs may prevent, delay, or reverse the development of resistance (17). Notable exceptions are lamivudine (3TC) and emtricitabine (FTC), with which a single point mutation can confer resistance in as little as 4 to 8 weeks when given as monotherapy or in combination with an antiretroviral regimen that does not fully suppress viral replication (e.g., dual NRTI therapy with zidovudine [ZDV]/3TC).

The prototype drug in this class, zidovudine, was approved in 1987. The designation nucleoside analog refers to the structural similarity of these drugs to the building blocks of nucleic acids (RNA, DNA) from which they differ by the replacement of the hydroxy (-OH) group in the 3' position by another group that is unable to form the 5' to 3' phosphodiester linkage essential for DNA elongation. Thus, NRTIs interfere with reverse transcriptase activity by competing with the natural substrates and incorporating into viral DNA to act as chain terminators in the synthesis of proviral DNA. To exert their antiviral activity, NRTIs must first be intracellularly phosphorylated to their active 5' triphosphate forms by cellular kinases. Because Tenofovir already contains a phosphate molecule in its structure, it only requires phosphorylation by cellular enzymes to its diphosphate form for its antiviral activity.
Currently, there are 8 individual NRTIs and 5 co-formulated products approved for the treatment of HIV. The production of one of the earlier NRTIs, zalcitabine, has been discontinued; it is no longer used in clinical practice because of its weak antiviral activity and unfavorable pharmacokinetic and toxicity profile. Kidneys are the primary route for elimination of all NRTIs. Thus, dose adjustment is required in renal insufficiency for all NRTIs with the exception of abacavir. One notable class wide adverse effect is mitochondrial toxicity, which is responsible for the clinical syndromes of lactic acidosis with hepatic steatosis, peripheral neuropathy, and lipoatrophy. Although this toxicity is a class wide toxicity, stavudine (d4T), didanosine (ddI), and zalcitabine (ddC) are the drugs most frequently associated with it. Lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC) are the NNRTIs with low mitochondrial toxicity potential.

Didanosine is eliminated by glomerular filtration and active tubular secretion (18). The renal clearance of didanosine is significantly greater than the glomerular filtration rate, indicating that renal tubular secretion of didanosine occurs. Compared with patients who have normal renal function, in patients with chronic renal failure, there are significant increases in the half-life and significant decreases in the total body clearance of didanosine. Didanosine is taken up by hOAT1 at the proximal tubules, and it is possible that competition between tenofovir and didanosine for the hOAT1 transporter produces an increase in the didanosine concentration, leading to an increased risk of mitochondrial damage and nephropathy. Co-administration of tenofovir with didanosine has resulted in a significant increase (28%) in maximum serum concentrations of didanosine, leading to an increased risk of didanosine toxicity (19). Hence, a reduction in the dosage of didanosine is recommended when it is coadministered with tenofovir (32).

Tubular dysfunction- NRTIs (for eg- didanosine and abacavir) (20, 21, 22) have been occasionally associated with Fanconi syndrome and nephrotoxic diabetes insipidus. Hence serum levels of potassium and magnesium ions should be monitored in patients with HIV receiving NRTIs.

AKI can develop with lactic acidosis secondary to NRTI-related mitochondrial cytopathy. Risk factors for lactic acidosis include extended duration of treatment, old age, female gender, pregnancy, hyper triglycerides, obesity, hepatitis C infection, impaired kidney function, treatment with ribavarin and alcohol use. Rabdomyolysis should be considered in patients with HIV who have AKI, particularly if they are being treated with Zidovudine or Didanosine (23, 24, 25, 26).

Nucleoside/nucleotide analog reverse transcriptase inhibitors and the kidney

Patients with HIV infection are at increased risk of drug-induced renal toxicity, most commonly associated with trimethoprim-sulfamethoxazole (TMP-SMZ), pentamidine, or acyclovir treatment. Nephrotoxicity is dose-limiting toxicity associated with the clinical use of nucleotide analogue reverse transcriptase inhibitors.

Evidence suggests that polymerase gamma, the DNA polymerase present in mitochondria, is inhibited by NRTIs/NtRTIs (27, 28, 29). It is thought that this leads to depletion of mitochondrial DNA (mtDNA) through inhibition of mtDNA synthesis. This depletion may contribute to toxicity associated with NRTIs/NtRTIs. Unusual, but significant, serious toxicities that can occur in patients exposed to these agents include lactic acidosis, hepatic steatosis, pancreatitis, myopathy, cardiomyopathy, peripheral neuropathy, and rapidly ascending muscular weakness. Interestingly, although some toxicity (e.g., lactic acidosis) may occur with all NRTI drugs, other toxicities (such as peripheral neuropathy) may predominantly occur with specific NRTIs, suggesting diverse mitochondrial effects of the drugs that may be dependent on varying ability to penetrate particular cell types. The relative potency of the NRTIs/NtRTIs in inhibiting polymerase gamma in vitro is highest for zalcitabine (ddC); followed by didanosine (ddI), stavudine (d4T), and ZDV; with the lowest potency for 3TC, abacavir (ABC), and tenofovir disoproxil fumarate (TDF) (14, 30). The prevalence of mitochondrial-associated adverse effects in children is unknown. A potentially fatal hypersensitivity reaction occurs in approximately 5% of adults and children receiving ABC. Before using ABC, patients must be cautioned about the risk of a serious hypersensitivity reaction and how to recognize symptoms. A genetic predisposition to this syndrome has been identified (HLA-B*5701) and patients with this HLA type should not be treated with ABC.

Tenofovir (Viread; Gilead) - represents the first of a new class of antiretroviral drugs, the nucleotide reverse-transcriptase inhibitors. It is the best studied culprit of kidney damage in HIV. Two similar acyclic nucleoside phosphonate antiviral derivatives, adeovir and cidofovir, have been associated with dose-limiting, renal tubular cell toxicity in patients with infectious hepatitis or cytomegalovirus infection who have been treated with these agents (31, 32, 33). In 2007 report, the cumulative tenofovir exposure was estimated to be 455,392 persons per year in Europe and North America (34). Tenofovir related kidney disease occurs generally in patients with predisposing renal illnesses or co morbidities such as diabetes (35).

Proposed mechanisms for this Tenofovir drug-induced proximal tubular toxicity include epithelial cell mitochondrial DNA depletion (16, 17) and/or direct tubular cytotoxicity (36). No direct association with mitochondrial toxicity has been found for tenofovir (37). Multiple drug interactions with tenofovir and other HIV drugs lead to renal tubular toxicity and tenofovir associated ARF (38). Tenofovir predominately accumulates in proximal renal
elevated serum creatinine level at a 24 month follow up after inception of tenofovir therapy (47). Irrespective of the low (0.5%-1.5%) incidence of potentially reversible tenofovir-related AKI, early detection of proximal tubule injury (as indicated by normoglycemic glucosuria, leukocyturia, proteinuria and low serum phosphate level) is critical to prevent irreversible chronic tubulointerstitial fibrosis (48, 49).

Adefovir- Fanconi's syndrome-is characterized by proximal renal tubular dysfunction and is associated with hyperaminoaciduria, glucosuria, and phosphaturia. Although serum glucose is typically within normal limits, other laboratory abnormalities are hypophosphatemia and hypouricemia. Fanconi's syndrome can be related to inherited or acquired conditions; iatrogenic causes are ifosfamide, cisplatin, tetracycline, aminoglycosides, valproic acid, and the acyclic nucleotide analogs cidofovir and adefovir.

Combination Therapy / HAART

The purpose of combination is to prevent viral replication in more than one mechanism to minimize the potential for viral mutations to escape inhibition. The choice of the combination should be one that provides a complementary viral inhibition, is convenient and is well tolerated. Highly Active Anti-Retroviral Therapy (HAART) consists of 3 or more highly potent anti-HIV drugs, commonly reverse transcriptase inhibitors and protease inhibitors. The principle that lies behind HAART is that a single drug therapy may be successful for a while, but because HIV changes to avoid detection, drug-resistant strains will often arise in the patient. The chances of a HIV genome mutating such that it can resist three separate drug treatments at once, however, is so small that the pressure of this therapy prevents the emergence of resistant strains.

HAART and antihypertensive drugs

No antihypertensive agents are currently contraindicated in patients receiving HAART. Nonetheless, Calcium channel blockers should be avoided. Protease inhibitors can increase serum concentration of calcium channel blockers below therapeutic levels and thereby leading to hypotension and bradycardia. While NNRTIs reduce serum concentration of calcium channel blockers below therapeutic levels. In addition, serum levels are increased by atazanavir, and the effects of metoprolol might be enhanced.

Conclusions

Every good thing in this world comes with its own side effects; hence even though ARV’s are life saving drugs for HIV/AIDS population, they are at times proved to have harmful effects.

HAART itself can cause renal toxic effects directly by inducing acute interstitial nephritis, crystal nephropathy and renal tubular dysfunction. Hence, it is important to remember that many patients may present with muscle wasting while they are receiving HAART. Renal abnormalities tend to develop in the setting of multiple
patients who are receiving tenofovir concomitantly with ritonavir or lopinavir-ritonavir, ritonavir plus didanosine, or ritonavir plus atazanavir. A significant increase in the serum creatinine level or new-onset renal tubular dysfunction during tenofovir therapy with ritonavir, lopinavir-ritonavir, ritonavir plus didanosine should lead one to immediately discontinue tenofovir treatment and to perform more-detailed assessments of renal function. Earlier recognition of tenofovir-associated acute changes in renal function can benefit on a large scale. Hence either avoidance to use of Tenofovir or if used under special precautions can decrease its renal toxicity effects. Fear of possible nephrotoxic effects is not a valid reason to withhold life saving antiretroviral therapy in HIV infected patients. Periodic evaluation can prove to lower advancing of renal damage.

References
1. Pediatric antiretroviral drug information Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection February 23, 2009


38. Viread (tenofovir disoproxil fumarate) [package insert]. Foster City, CA; Gilead Sciences, 2005.


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