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# Highly Active Antiretroviral Therapy: The Issues and Factors Deciding Adverse Drug Reactions

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ABSTRACT

Antiretroviral agent (ARVs) has predictable toxicities and adverse effects because they are most chronically administered drugs. It is essential that clinicians noticeably understand ADRs, eagerly identify them in patients and manage them successfully. Information on adverse drug reactions (ADRs) associated to antiretroviral (ARV) use in public health practice is signifying the requirement for ART safety surveillance in clinical care. In this article, we review the adverse effects of HAART therapy, with definite concentration to the issues and factors deciding adverse drug reactions. Our aspire is to assist physicians achieve a working knowledge of these adverse effects, with the definitive purpose of improving the tolerability and effectiveness of HIV treatment, promoting the early identification and setback of potentially serious adverse effects, and dropping the potential for adverse drug interactions.

**Keywords:** Adverse drug reactions, antiretroviral agents, anti-retroviral toxicities, highly active antiretroviral therapy, multi-drug therapy

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## INTRODUCTION

Ingress of HIV into body leads to sophisticated viral replication, immunosuppression, resistance and persistence making HIV a fatal condition. As a consequence, ultimate multi-drug therapy is essential for whole restraint of HIV replication. There are many drugs available in various drug classes and choosing between many of these combinations is progressively more dependent upon familiarity of anti-retroviral toxicities. The preamble of highly active antiretroviral therapy (HAART) has led to a momentous decline in AIDS-related morbidity and mortality.[1] Antiretroviral agent (ARVs) has predictable toxicities and adverse effects because they are most chronically administered drugs. Adverse drug reactions (ADRs) array from mild to life threatening with short and long term effects. [2] The range of adverse effects related with ARVs may differ between developed and developing countries.[3]

Studies on the incidence of ADR have reported the range between 11%-35.9% with incidence as high as 54% in the existence of opportunistic infection. Incidence of harsh ADR has been reported to be as high as 10% with a study observing an incidence rate of 8 per 100 person years. [4-6] In a appraisal of above 1000 patients in a Swiss cohort that received combination ARV therapy, 47% and 27% of the patients were reported to have clinical and laboratory adverse events. [7] The long term effects of ARTs are chiefly unfamiliar but current research provides insights into some ADRs of ARV and includes peripheral neuropathy and lipodystrophy allied with stavudine, [8,9] anaemia related with zidovudine [10,11] and nevirapine based hepatotoxicity and rash [12.] Incidence of hepatotoxicity was pragmatic to be 16% and 8% for patients on nevirapine and efavirenze[13] although incidence of anemia ranged from 3- 12% among patients on zidovudine in developing countries.

Regrettably, up to 25% of patients cease their primary HAART regimen because of treatment failure, toxic effects or noncompliance within the earliest 8 months of therapy.[14] numerous strategies have been implemented to advance treatment duration. [15] Despite the fact that advances of new antiretroviral agents continues, efforts to take advantage of the effectiveness of presently obtainable treatments comprise attempts to better realize and handle adverse effects. There is extensive evidence concerning treatment success to adherence to ARVs. Conversely adherence to treatment is strictly linked to adverse drug reactions. It is essential that clinicians noticeably understand ADRs, eagerly identify them in patients and manage them successfully. [16] Information on adverse drug reactions (ADRs) associated to antiretroviral (ARV) use in public health practice is signifying the requirement for ART safety surveillance in clinical care.

In this article, we review the adverse effects of HAART therapy, with definite concentration to the issues and factors deciding adverse drug reactions. Our aspire is to assist physicians achieve a working knowledge of these adverse effects, with the definitive purpose of improving the tolerability and effectiveness of HIV treatment, promoting the early identification and setback of potentially serious adverse effects, and dropping the potential for adverse drug interactions.

**Classification of ARV**

1. Nucleoside Reverse Transcriptase Inhibitor (NRTI):
    - Zidovudine
    - Lamivudine
    - Stavudine
    - Didanosine
    - Zalcitabine
    - Abacavir
    - Emtricitabine
2. Nucleotide Reverse Transcriptase Inhibitors (NtRTI): Tenofovir
3. Non - Nucleoside Reverse Transcriptase Inhibitors (NNRTI):
    - Nevirapine
    - Delavirdine
    - Efavirenz
4. Protease inhibitor (PI):
    - Saquinavir
    - Ritonavir
    - Indinavir
    - Nelfinavir
    - Amprenavir
    - Lopinavir
    - Ritonavir
    - Atazanavir
    - Fosamprenavir
5. Fusion Inhibitors: Enfuvirtide

The dosages and adverse effects of antiretroviral medications are listed in figure 1 and 2.

| Drug | Abbreviation | Dosage | Most common adverse effects | Comments |
|---|---|---|---|---|
| **Nucleoside reverse transcriptase inhibitors (NRTIs)** | | | | |
| Zidovudine | AZT | 400–600 mg/d, divided (i.e., administered bid) | Nausea, headache, rash, anemia, leukopenia, elevation of liver enzyme levels, elevation of lactic acid level, elevation of CPK level | Should not be combined with d4T |
| Lamivudine | 3TC | 150 mg bid | Neutropenia (rare) | |
| Didanosine | ddI | Body weight 35–49 kg: 100 mg bid<br>Body weight > 50 kg: 200 mg bid | GI intolerance, pancreatitis, gout, reversible peripheral neuropathy | Should not be combined with ddC. Should be taken separately from food. Full daily dose can be given once daily |
| Didanosine-EC | ddI-EC | Body weight > 50 kg: 400 mg once daily | | |
| Zalcitabine | ddC | 0.75 mg tid | Reversible peripheral neuropathy, mouth ulcers, pancreatitis | Should not be combined with d4T or ddI. Relatively weak risk–benefit ratio limits usefulness |
| Stavudine | d4T | Body weight 40–60 kg: 30 mg bid<br>Body weight > 60 kg: 40 mg bid | Reversible peripheral neuropathy, lactic acid elevation (rarely fatal) | Should not be combined with AZT |
| Tenofovir | TDF | 300 mg once daily | GI upset, low phosphate levels | |
| Abacavir | ABC | 300 mg bid | Hypersensitivity reaction, which may be characterized by fever, rash, myalgias, arthralgias, malaise | Reaction may be fatal if medication is continued or patient is rechallenged |
| **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** | | | | |
| Nevirapine | NVP | 200 mg once daily for 2 wk, then increase to 200 mg bid | Rash, elevation of liver enzyme levels | Full daily dose can be given once daily |
| Delavirdine | DLV | 400 mg tid | Rash | |
| Efavirenz | EFV | 600 mg once daily (or 300 mg bid) | Central nervous system toxicity ("hangover," drowsiness), rash | |

**Figure -1: Nucleotide and non-nucleotide reverse transcriptase inhibitors and their adverse effects**

| Drug | Abbreviation | Dosage | Most common adverse effects | Comments |
|---|---|---|---|---|
| **Protease inhibitors (PIs)*** | | | | |
| Saquinavir | SQV | | | |
| Brand Invirase | INV | Administer with RTV, with SQV/RTV ratio as follows: 400 mg/400 mg bid or 1000 mg/100 mg bid or 1600 mg/100 mg once daily | Elevation of liver enzyme levels | Very poor bioavailability unless combined with RTV. Better tolerability (e.g., GI) and similar pharmacokinetics to FTV when us with RTV boosting |
| Brand Fortovase | FTV | 1200 mg tid. Alternatively, administer with RTV, with SQV/RTV ratio as follows: 1000 mg/100 mg bid or 1600 mg/100 mg once daily | GI toxic effects, elevation of liver enzyme levels | Better bioavailability than INV in t absence of RTV |
| Ritonavir | RTV | 600 mg bid | GI upset, diarrhea, circumoral paresthesias, elevation of liver enzyme levels, hypertriglyceridemia | Most common use at present is as PI booster at low doses (e.g., 100–400 mg/d) |
| Indinavir | IDV | 800 mg tid. Can be given with RTV boosting: IDV 800 mg/RTV 100 mg bid | Elevation of liver enzyme levels, nephrolithiasis, hypertension, ingrown toenails, benign hyperbilirubinemia | |
| Lopinavir/ritonavir | LPV/RTV | 3 capsules bid | GI upset | Two drugs combined in a single capsule. Dose should be increased to 4 capsules bid if used with EFZ NVP and in the presence of moderately to highly PI-resistant HIV virus |
| Amprenavir | APV | 1200 mg bid. Can be given with RTV boosting: APV 600 mg/RTV 100 mg bid | Rash, GI upset | |
| Nelfinavir | NFV | 750 mg tid | GI upset, mostly diarrhea | |

Note: bid = twice daily, tid = 3 times daily, CPK = creatine phosphokinase, GI = gastrointestinal, EC = enteric coated.
*PIs have multiple drug interactions and may be associated with various metabolic adverse effects such as diabetes mellitus, hyperlipidemias or lipodystrophy (limb and face wasting and accumulation of abnormal fat deposits).

**Figure -2: Protease inhibitors and their adverse effects**

**Issues**

**1. Pharmacoeconomic issue**

Although the access to ARV is escalating because of sinking cost only 5-10% of patients in require for ARV are on ARV.

**2. Gender Discrimination**

The implication of when to initiate ARV is similar for HIV infected adult male and female patients and the sex specific differences in CD4 counts, viral load and rate of disease progression are similar but the numeral of females who really take ARV are incredibly little. [17]

**Adherence**

HIV viral restraint, condensed rates of resistance and improved survival has been associated with elevated rates of adherence to ARV. Hira et al reported adherence of more than 95% in 50-60% of cases and the majority significant factor ensuing in nonadherence is toxicity. [18]

**Drug-Drug Interaction**

E.g. Oxidative metabolism of nevirapine is in the liver by cytochrome P450 isoforms CYP3A4 and CYP2B6. Rifampicin induces the synthesis of CYP3A4 and therefore decreases nevirapine levels by 20-58%. So, employ of this combination is not optional; but if used, co-administration should be done with cautious monitoring.

**Drug-Food Interaction**

The oral bioavailability of definite ARV is affected if administered with food.

**Other issues**

While deceitful the regimen along with toxicities additional issues to be kept in mind are resistance, treatment failure and deliberation for future options.

**Factors deciding ADR**

1. Pharmacogenomics- This is the study of how people with diverse genetic makeup react another way to particular drugs. The expectation is that it will lead to high precision prescription, with less side effects & enhanced outcomes.
2. Sex- Female patients have a superior tendency of developing SJ Syndrome and symptomatic hepatic events from Nevirapine
3. Stage of HIV- Ex. HIV infected women with CD4 counts > 250 cells/mm3 are at a 12-fold augmented risk and men with CD4 counts > 400 cells/mm3 have a 3-fold greater risk for Nevirapine related over toxicity than with CD4 counts below this threshold.
4. Co-administration of other drugs
5. Co-existing infection / opportunistic infections [19]

**Adverse drug reactions**

Anti-retroviral agents can lead to short-term toxicities or long-term side effects.

Short-term toxicities:

1. Organ: Liver, kidney, bone marrow

2. Cutaneous Reactions: SJ syndrome, hypersensitivity

Long term side effects:

1. Morphologic complications

- Lipoaccumulation / lipohypertrophy, visceral adiposity
- Breast enlargement
- Dorso-ventral fat pad
- Lipomas
- Cosmetic disfigurement

2. Metabolic Abnormalities

- Dyslipidimias
- Abnormalities of glucose metabolism
- Insulin resistance
- Lactic acidosis
- Hepatosteatosis
- Osteonecrosis, osteopenia, osteoporosis
- Increasing bleeding in hemophiliacs

Antiretroviral therapy can have an extensive array of adverse effects on the human body (Figure. 1)

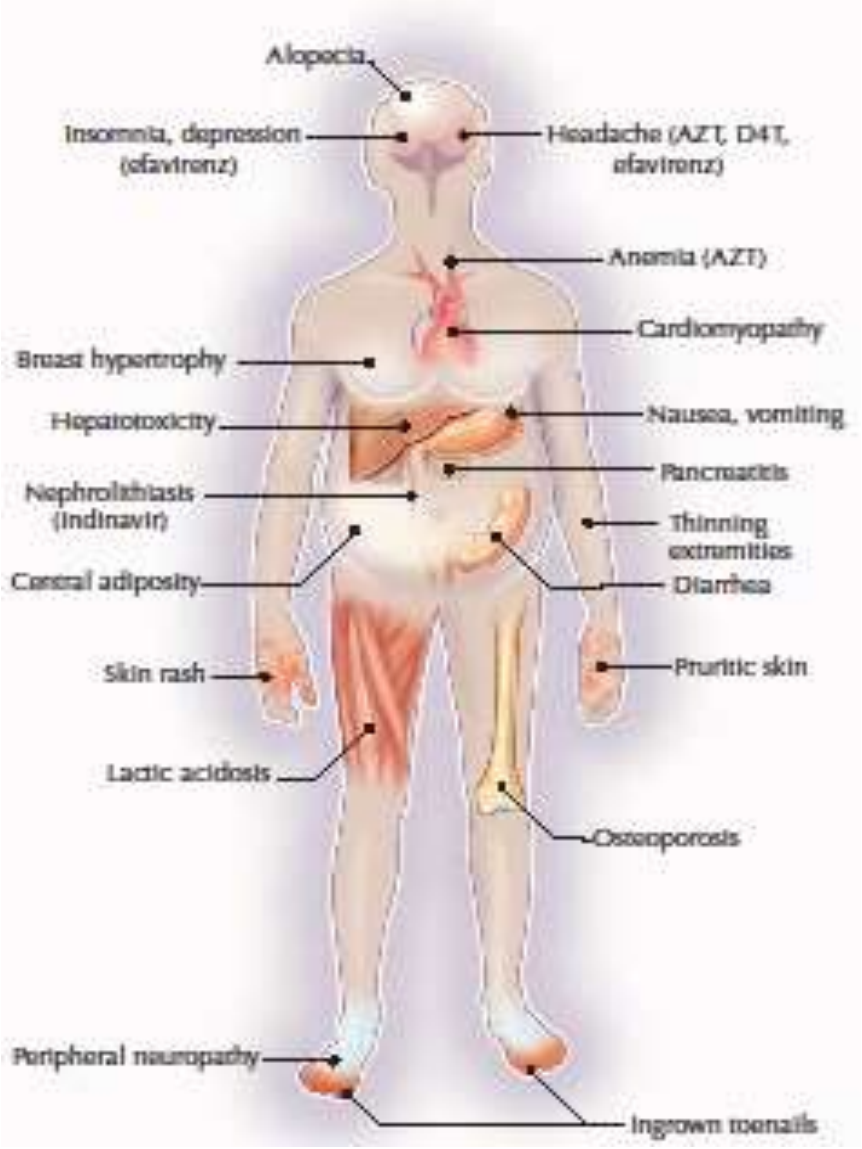


**Figure. 1: Adverse effects of antiretroviral therapy**

In some cases, only a certain drug causes the effect (drug name in parentheses).

**Mitochondrial toxicities**

The medium and long-term side effects are due to inhibition of mitochondrial DNA polymerase ensuing in impaired synthesis of mitochondrial enzymes that produce ATP by oxidative phosphorylation.

- Myopathy – Zidovudine
- Neuropathy – Stavudine, Didanosine, Zalcitabine
- Hepatic-steatosis and lactic academia - Stavudine, Didanosine, Zidovudine
- Peripheral neuropathy – All NRTIs predominantly Stavudine
- Pancreatitis - Didanosine

Main serious mitochondrial toxicities are lactic acidosis and pancreatitis. Mortality was 80% when lactate concentration was greater than 10 mmol/L.

Lactic acidemia is about15% and is frequently related with mild legitimate symptoms, mild raise in liver enzymes and peripheral lipoatrophy.

Clinical manifestations:

Muscle: Fatigue, myalgia, proximal weakness, wasting

Heart: Dilated cardiomyopathy

Nerve: Distal pain, numbness, paraesthesia, reduced reflexes/power

Liver: Hepatomegaly, nausea, ascites, edema, dyspnoea, encephalopathy

Pancreas: Abdominal pain

Fat: Peripheral lipoatrophy, Lipomata

Management: Management of mitochondrial toxicities is usually partial to termination of causative drug. Given that toxicity can be of late onset, clinical screening for drug toxicity should be done during therapy. [20]

**Hypersensitivity**

Drug hypersensitivity in HIV infected patients is about 100 times more frequent than in general population. Rash is the majority prominent on body and arms and begins after 1-2 weeks of therapy. SJ syndrome or Toxic Epidermal Necrolysis (TEN) develops in less than 0.3% of patients[21]. All NNRTI (Nevirapine, Delavirdine, Efavirenz), NRTI (Abacavir) and PI (Amprenavir) that cause hypersensitivity.

Clinical Features

Principal Features

- Morbilliform / maculopapular rash
- Fever (often precedes rash)
- Myalgias, fatigue
- Mucosal ulceration

Less common features (< 5%)

- SJ syndrome/TEN
- Anicteric hepatitis
- Hypotension
- Acute interstitial nephritis
- Acute interstitial pneumonitis

About 50% of ARV hypersensitivity resolves suddenly regardless of continuation of therapy. Treatment should be congested if there is mucosal participation, blistering, exfoliation, clinically considerable hepatic dysfunction (e.g. aminotransferase concentrations greater than five times baseline), fever (> 39oC or intolerable prutiritus). [22] Rechallenge is possible for mild to moderate NNRTI hypersensitivity but not for abacavir.

**Lipodystrophy Syndrome**

In general prevalence is about 50% after 12-18 months of therapy. In adult males, there is a generally fat loss even though fat accumulation may outweigh in women.

Metabolic Features:

- Hypetriglyceridemia
- Hypercholesterolemia
- Insulin resistance (increased insulin, C-peptides)
- Type-2 diabetes mellitus / impaired glucose tolerance
- Lactic academia

Risk factors for lipodystrophy are genetic factors, raised C-peptides, low body weight before therapy and triglyceride concentrations after about 1 year.

Management:

- Low fat diet and aerobic exercise – may aggravate lipoatrophy
- Testosterone replacement therapy
- Subcutaneous or intralesional growth hormone
- Thiazolidinediones: Metformin, Gemfibrozil and Atorvastatin
- Anabolic steroids
- Restorative surgery (excision or liposuction)
- Withdrawal or substitution of ARV

Mc Comsey GA et al reported upgrading in lipodystrophy related with ARV in patients who were switched from Stavudine to Abacavir or Zidovudine.[23]

**Cutaneous manifestations**

NNRTIs have resulted in different cutaneous eruptions, as well as a hypersensitivity syndrome. NRTIs have resulted in alterations of the nails and mucocutaneous pigmentation, vasculitis, hair changes, and morbilliform eruptions.

**Table-3: Summary of cutaneous drug reactions**

| DRUG | CUTANEOUS REACTIONS |
|---|---|
| Protease inhibitors (in general) | 1. Lipodystrophy<br>2. Hypersensitivity reaction<br>3. Acute generalized exanthematous pustulosis |
| Indinavir | 1. Acute porphyria<br>2. Stevens-Johnson syndrome<br>3. Drug eruption<br>4. Gynecomastia<br>5. Alopecia<br>6. Paronychia with nailfold pyogenic granuloma-like lesions |
| Ritonavir | 1. IgA-mediated hypersensitivity reaction<br>2. Drug reaction<br>3. Hematoma formation |
| Nelfinavir | 1. Morbilliform eruption<br>2. Generalized urticaria |
| Saquinavir | 1. Gynecomastia<br>2. Fixed drug reaction<br>3. Stevens-Johnson syndrome<br>4. Hypersensitivity syndrome (DRESS) |
| Delavirdine | 1. Drug eruption |
| Zidovudine | 1. Nail hyperpigmentation<br>2. Mucocutaneous hyperpigmentation<br>3. Hypertrichosis<br>4. Eyelash hypertrichosis<br>5. Hypersensitivity syndrome<br>6. Leukocytoclastic vasculitis<br>7. Heightened reaction to mosquito bites<br>8. Paronychia with lateral nailfold pyogenic granuloma-like lesions |
| Didanosine | 1. Leukocytoclastic vasculitis<br>2. Stevens-Johnson syndrome<br>3. Papuloerythroderma of Ofuji<br>4. Acute gouty arthritis<br>5. Alopecia |
| Lamivudine | 1. Allergic contact dermatitis<br>2. Paronychia with lateral nailfold pyogenic granuloma-like lesions |
| Zalcitabine | 1. Morbilliform eruption<br>2. Hypersensitivity syndrome |

**Gastrointestinal Effects**

All ARV can cause nausea, vomiting or diarrhea early in treatment. Nausea is more frequent with Zidovudine and Didanosine. Indinavir is also related with esophageal reflux (about 3%) but should not be given with antacid and prevent its absorption because salts in the antacids can combine with Indinavir. H2 blockers and proton pump inhibitors are suitable options.

Several epidemiological studies recommend that the risk of myocardial infarction increases with extent of exposure to combination antiretroviral therapy containing NNRTI / PI which are notorious to cause metabolic complications like hyperlipidemia and insulin resistance. PI / NNRTIs may be substituted by 3 NRTI regimen. [24]

**Hepatitis**

NNRTIs can cause hepatitis in the initial 2-3 months of treatment, occasionally as a part of hypersensitivity reaction. NRTIs can cause hepatic steatosis, usually subsequent to 6 months of therapy, possibly via mitochondrial toxicity. Protease inhibitors can too cause hepatitis but the mechanism is unknown, predominantly in patients coinfected with hepatitis B or C, raised hepatic aminotransferase concentrations and alcoholism. [25]

**Osteonecrosis/avascular necrosis**

Many patients have additional risk factors, including alcohol abuse, testosterone therapy, hyperlipidemia, corticosteroid use, lipid lowering agents and hypercoagulability. [26]

**Pregnancy**

No antiretroviral agents have been rated by the Food and Drug Administration as category A.[27-29]

Drugs rated as categories B are didanosine, saquinavir, ritonavir and nelfinavir.

Drugs rated as category C are delavirdine, zalcitabine, nevirapine,lamivudine,stavudine and zidovudine.

**Immune reconstitution syndrome (IRIS)**

Immune reconstitution inflammatory syndrome (IRIS) is a consequence of an exuberant inflammatory response towards formerly diagnosed or incubating opportunistic pathogens, as well as response towards other as until now undefined antigens[30]. This includes inconsistent exacerbation of pulmonary and CNS mycobacterium tuberculosis infection, cytomegalovirus retinitis, toxoplasmosis, chronic active hepatitis, herpes zoster and psoriasis. Treatment for this disorder includes maintenance of initial therapy, continuance of effective HAART, careful use of anti-inflammatory agents.

**General principles of management of antiretroviral drug toxicity**

**Drug Initiation**

1. Initiate drugs with non-overlapping toxicities and minute risk of interaction with obtainable therapy
2. Consider clinical setting:
    - Pregnancy/ Pediatric age group
    - Injecting drug user
    - Chronic hepatitis B or C
    - Hemophilia
    - Post exposure prophylaxis
3. **Adverse reaction**

- Dose reductions not advised because of possible for drug resistance
- In patients with excellent control of viral replication: If possible, instantly change to drug with diverse toxicity profile. Discontinue all drugs, mainly if harsh reaction, then judge new regimen with diverse toxicity profile.
- In patients with unmanageable viral replication: Discontinue accompanying drug; start new agent with unlike toxicity profile[31].

**Post adverse reaction**

- Rechallenge should be medically supervised but is contraindicated with hypersensitivity to: Abacavir / Mucosal participation / Grade 3-4 rashes.
- Desensitization possibly improper because of probable for initiation of viral resistance.

**Monitoring of patients who are receiving antiretroviral agents**

- Regular laboratory monitoring should be made around every 3 months to establish whether the patient has asymptomatic abnormalities.
- Monitoring laboratory tests comprise complete and differential blood counts and measurement of creatinine, electrolyte, liver transaminase, bilirubin and amylase levels.
- Patients should too be monitored at regular intervals for dyslipidemia, diabetes, and lipoaccumulation or lipoatrophy.
- Imaging tests, such as abdominal CT to identify visceral fat, are not optional for routine monitoring[32-33].

## CONCLUSION

Prolonged treatment with combination regimens can be complicated to uphold because of troubles with adherence and toxic effects. The risk of precise side effects varies from drug to drug, from drug class to drug class, and from patient to patient. An improved considerate of the adverse effects of antiretroviral agents is of concern not only for HIV specialists, but also for further physicians who care for HIV positive patients.

## ABBREVIATIONS

Adr's- Adverse drug reactions

AIDS - Acquired Immune-Deficiency Syndrome

ARV- antiretro viral agents

HIV- human immunodeficiency virus

HAART- highly active antiretroviral therapy

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