University
of
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Inaugural Lecture

HIV Drugs, Magic bullets, Time Bomb or useful poisons?: Towards their quality use in Limpopo Province.

Chapter 1

Introduction

The introduction of antiretroviral drugs, ARVs, as part of Human Immunodeficiency Virus, HIV clinical care has made Acquired Immunodifeciency Disease Syndrome, AIDS, a manageable chronic illness resulting in an individual's restored economic productivity and social functioning. Access to good quality antiretroviral treatment, ART has transformed the prediction as to the probable course and outcome of HIV/AIDS. Unfortunately these effects have been seen largely in settings where resources were available to make the drugs affordable and where there are health services capacities to optimize their sustained, safe and effective use. In resource poor settings these beneficial effects have been demonstrated in situations where there were strict controls. These controlled operational studies have shown that, there are multiple requirements for such ARVs beneficial effects to be realized and these can be grouped into three areas:

1. **the drugs**
2. **the client**
3. **the health system**

The health system needs to address the following simultaneously:

- Training health teams in both the public and private sectors, with regular updates on treatment and care options
- Recognizing services to **integrate HIV care** in outpatient departments and at health centres to allow for space, privacy and time and linkages with TB-DOTS and STI programmes
- Strengthening rapid registration of new drugs and **drug procurement and management systems** to ensure continuous availability of the drugs and avoidance of pilferage and misuse.
- Expanding and integrating **quality VCT** into the health system as an entry point to prevention
- Strengthening and upgrading **laboratory facilities.**

- **Communicating** to the public at large on the benefits and risks of ART.
- **Strengthening prevention programmes** to link closely with care and ART programmes and reinforce the need for prevention as primary goal within and beyond the health sector

In addition to these requirements there is a need for those who will handle the drugs to have adequate knowledge about:

- **the drugs**
- **the client**
- **the virus and related microorganisms**

Resistance of HIV-1 to ARVs is a widespread problem that limits the efficacy of antiretroviral treatment. High prevalence of genotypic and phenotypic HIV-1 drug resistant strains were found in patients receiving antiretroviral therapy, ART in Abidjan and the reason was poor use by the patients or suboptimal administration of the drugs by the physicians (Adje et al 1999). The first case of HIV-1 transmission with reduced susceptibility to an ARV, zidovudine, AZT, was reported in 1989 (Larder et al 1989). Subsequently, several reports documented the transmission of HIV-1 with reduced susceptibility to other Non-nucleoside Reverse Transcriptase Inhibitors, NNRTIs or Protease Inhibitors, PIs in patients with acute and early HIV-1 infection. Ever since the introduction of potent combination regimens, transmission of multi-drug resistant HIV-1, with reduced susceptibility to several ARVs in different pharmacological groups has been reported (WHO, 2000).

Given that the 5.3 million people in South Africa are living with HIV and of these 104, 000 are on ART and 840 000 need ART the questions that needs urgent attention in Limpopo Province before scaling up access, are:

- **Is HIV Resistance to any of the front line drug regimen occurring ?**
- **Is the resistance spreading?**
- **What are the reasons for the spread?**
- **How much do we know about the virus and its transmission dynamics?**

These are pertinent questions that require answers in order to make sure that ARVs are used properly . ARVs are now available on the open market. People living with HIV and their families are going to great lengths to get these MAGIC BULLETS. There are no controls, in terms of access and what is going on is "therapeutic anarchy".

Chapter 2

From GRID to AIDS – The transmission dynamics understood

a) The virus

In 1981 in the US, a new, or newly recognized, condition of immune deficiency had entered the male homosexual population, and already the doctors involved with the patients were wondering what the new factor might be, what had changed. In those early days, it was called GRID, or Gay-Related Immune Deficiency. Before the year end, clusters of similar cases were beginning to be seen among nonhomosexual groups, Haitians in particular, intra-venous drug users, IVDUs, haemophiliacs treated with the clotting Factor VIII, and recipients of blood transfusions and children born to IVDUs. People started to refer to the "Four Hs" – homosexuals, heroin-users, haemophiliacs and Haitians / heterosexuals or *Homo sapiens.* Edward Hooper (1999) in his

book "The River" put it aptly why one of the Hs should be *Homo sapiens* and I quote:

> ***"Everyone who has ever had sex, who has ever received a blood product or a jab with unsterilized needle, is potentially at risk – and for those who prefer to live their lives in the harsh glow of divine judgement and retribution, than the sins of the fathers can indeed be said to have been visited on the sons (having called on the mothers first). Indeed, one of the greatest tragedies of this new and horrible condition is that it all too swiftly brings out the stentorian language of blame and accusation, especially among those, by their own lights, should know better"***

As time went by people began to realize that GRID was not just a gay disease. It was an Acquired Immune Deficiency Syndrome, or AIDS. "Acquired" indicated at the time that the causative agent was unknown but was transmitted from one human being to the other. "Syndrome" meant that there was a range of symptoms associated with the infection, rather than a single disease presentation.

It was in late 1983 that Professor Luc Montagnier and his team from the Pasteur Institute in Paris that they identified a RETROVIRUS in the blood of people with AIDS and swelling and inflammation of the glands. The virus at the time was christened "LAV", Lymphadenopathy-Associated Virus. Another team in San Francisco isolated it from AIDS patients and call it ARV or AIDS-Related Virus. At the National Institutes of Health, Professor Robert Gallo, nearly a year later announce that they have identified the AIDS agent and they call it HTLV-III because of its presumed identity with other two ONCOVIRUSES, Human T-Cell Lymphotropic Viruses that Gallo had already discovered. It later

got rechristened as HIV, the Human Immunodeficiency Virus, as we know it today and the scientific and public perceptions of AIDS have steadily broadened. It was in April 1984, that Robert Gallo told America that he had found the 'probable' cause of AIDS. Within two years there was general consensual acceptance of Gallo's hypothesis which was transformed into a universal scientific tenet, that HIV was the sole cause of a number of AIDS – defining illnesses. The drug azidothymidine, AZT, the first drug licenced as anti-retroviral, played a crucial role in reinforcing Gallo's idea (Walker, 1997) of HIV an RNA virus to be responsible for AIDS.

The RNA is a single stranded diploid 100 – 120 nm in diameter. Its basic gene structure has *gag* (core protein), *pol* (polymerase / reverse transcriptase) and *env* (envelope protein) genes. Additional proteins are said to regulate viral protein synthesis. CD4 antigen is the receptor for the virus; it is present on $CD4^+$ T lymphocytes and cell of the monocyte / macrophages lineage. Viral gp 120 binds to CD4 but chemokinetic receptors are involved in the subsequent gp41-mediated fusion and internalization. Since HIV is a retrovirus comprised of RNA (rather than the more usual genetic material, DNA) it uses the enzyme, reverse transcriptase, RT, to convert the RNA to DNA so that it can be incorporated into the host cells resulting in immune dysfunction i.e Immune deficiency. The immune deficiency comes about because of the depletion and functional impairment of the $CD4^+$ T-cell subset over time. Several mechanisms as to how this comes about have been proposed. They include:

- Accumulation of RNA and unintegrated DNA in the cell cytoplasm
- Intracellular binding of CD4 and gp120 (Infected cells may bind to uninfected cell by gp120-CD4 linkages)
- Binding of gp120 protein to the surface of uninfected $CD4^+$ T cells making them vulnerable to antibody-dependent cell mediated cytotoxicity while infected cells may be killed by gp120-specific cytotoxic T cells.

- HIV proteins acting as superantigens, resulting in vast expansion and then exhaustive depletion of cells.
- Induction of T-cell apoptosis and viral budding leading to cell membrane weakening and lysis

The spectrum of immune dysfunction is therefore characterized by many things.

Modelling of the plasma virus (Viral Load, VL) and $CD4^+$ T-cell responses to antiretroviral therapy, ART suggests that the average half-life of the virus and infected cells in circulation is less than two days. 10^9 - 10^{10} viruses are released from infected cells and similar numbers of new cell are infected and die daily (Roitt et al 2001).

b) HIV / AIDS Natural history

- The initial infection with HIV is a subclinical type of infection and may not be of much consequence. A small part of the infection may develop within 2-3 weeks. This is manifested as transient illness similar to glandular fever, with general feeling of illness or discomfort, muscle pains, swollen lymph nodes, sore throat and rash. Opportunistic infections, OIs, are not seen at this stage. A large majority of people remain asymptomatic. The majority of those infected do not give a history of this infection because it goes unnoticed resembling routine infections.
- Then there is the asymptomatic phase of the infection where most of the patients still maintain normal health and are unaware of the disease. The CD4 count is usually above 500 cells / mm^3. This phase has a duration of several years – median duration being 10 years. In southern Africa sexual transmission is the major route (Walker, 2006) and some ARV resistant strains have been reported to show greater transmission than others (Seriano et al 2004).
- Later on infection symptoms including fevers, night sweats, recurrent diarrhoea and weight loss occur, together with

'minor' conditions that largely affect the mucous membranes and skin: for example oral candidiasis (thrush), shingles, recurrent anogenital herpes simplex and a variety of skin infections. During this period the CD4 cell count continues to come down. This is the time recommended to initiate ART. These conditions often signal the development of serious OIs and tumours, which constitute AIDS when the CD4 count is, usually, below 200 cells / mm^3. It is important to note that most of the OIs are due to reactivation of latent organisms in the host or, in some cases ubiquitous organisms to which we are continually exposed. They are difficult to diagnose and treatment often suppresses rather eradicates them. Relapses are common and continuous suppressive or maintenance treatment is necessary.

Three main organ systems are affected:

- **The respiratory system; *Pneumocystis carinii, Mycobacterium tuberculosis.***
- **The Gastrointestinal tract; *Crytosporidium(a protozoa), Salmonella, Campylobacter***
- **The nervous system; *Cryptococcus neoformans***

- In advanced HIV disease state the CD4 cell count is less than 50 cells / mm^3. The patient usually has multiple OIs infection and malignancies. The majority of patients in our setting are seen at this late-stage of the disease (De Cock, 2006). With increase use of ART the survival among the advanced HIV disease patients has improved.

Chapter 3

The magic bullets

In ART both the VL (serum HIV RNA levels) and CD4 counts are important prognostic makers to be monitored (Mellors 1997). In

other words VL and CD4 count can help in the prediction as to the probable course and outcome of HIVAIDS. The optimal time to start ART remains unclear, but most practitioners act on a repeatedly low CD4 count of 200 – 400 cells / μl^{-1} and in all HIV infected persons who are symptomatic. ARVs should also be reserved for the following individuals:

- Rape victims
- Health care providers
- Pregnant women

ARV treatment goals are ;

- **Maximal and durable suppression of the viral load**
- **Restoration and preservation of the immunological function**
- **Improvement of quality of life**
- **Reduction of the HIV-related morbidity and mortality**

Highly Active Antiretroviral Therapy, HAART - which is achieved by combining at least three drugs from various classes of ARVs into a "cocktail" to be taken daily - is the recommended treatment for HIV infection. The drugs used have specific vulnerable "receptors" in the virus.

Paul Ehrlich while experimenting with arsphenamine (Salvarsan) which he was attempting to develop for syphilis introduced the idea that a drug might act as **"magic bullet"** which went for a vulnerable "receptor". Such a receptor could be an enzyme, as is the case for ARVs.

The front line drug regimen recommended in South Africa include;

- **Protease Inhibitors (Pis);**
  - *Ritonavir*

Uninhibited reverse transcription of viral RNA, once internalized into the CD4 cell, results in the production of double-stranded DNA. This is inserted into host genome as the HIV provirus, by a virally coded integrase enzyme (no magic bullet for this enzyme yet !). Cell activation leads to transcription and the production of viral messenger RNAs. Structural proteins are produced and assembled. It is the production of these structural proteins which is inhibited by proteases like *ritonavir.*

- **Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs);**
  - *Efavirenz and Nevirapine*

The NNRTI based HAART is safe and effective, in general, and it has been shown to ameliorate the toxicities (Such as hyperglycaemia and lipid abnormalities) associated with PI-based HAAT (Boyle, 2000)

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs);**
  - *Didanosine, Lamivudine, Stavudine and Zidovudine*

As indicated earlier, HIV is a retrovirus comprised of RNA (rather than the more usual genetic material, DNA). It uses the enzyme, reverse transcriptase, RT, to convert the RNA to DNA so that it can be incorporated into the host cells resulting in immune dysfunction i.e Immune deficiency.

A nucleoside is a glycoside resulting from the removal of phosphate from a nucleotide. It is a combination of a sugar, ribose, in the case of mammalian cells linked to a pyrimidine (cytosine and thymine) or purine (adenine and guanine) base of the RNA or DNA molecule. NRTIs are analogues of these nucleoside that inhibit the reverse transcriptase enzyme. For example AZT is an analogue of thymine and was the first drug o be introduced for HIV infection.

Chapter 4

The story of AZT

AZT was not designed as a drug to combat an HIV. It was developed, from a herring and salmon sperm extract, by Jerome Horowitz in 1964 for the National Cancer Institute (NCI). As cancer chemotherapy, it was designed to destroy dividing cells which were producing tumours. **AZT was, however, indiscriminately cytotoxic. It could kill any dividing cells by interfering with the reproduction of DNA.**

After development of AZT was dropped it became an 'orphan drug', one with no pharmaceutical company parent to rear it and it languished, on the shelves of the National Institutes of Health. The decision to test AZT in 1985 for anti-viral properties was not due to farsightedness or any sixth sense -- in 1985 and 1986, inside NIH research establishments everything which came to hand was being tested for antiviral qualities.

AZT was sent to Burroughs Wellcome where Dave Barry, head of research, suggested that AZT should be sent to an investigator to be tested for anti-retroviral qualities. The commissioned report was positive. Wellcome then put the drug in the hands of Sam Broder, head of the National Cancer Institute (NCI) -- part of the National Institutes of Health (NIH). Since 1984, Broder had been Clinical Director of the NCI Special Task Force on AIDS.

Burroughs Wellcome had two good reasons for giving the drug to Sam Broder -- first Robert Gallo worked at the NCI and secondly, Wellcome knew that Broder would see the drug through the regulatory hoops. With Wellcome apparently playing a back seat role, the drug became the official cure for AIDS, promoted by the US government. To help Broder work AZT through the regulatory process, and to secure their ownership of the drug, Burroughs Wellcome gave the NCI $55,000 in 1985 and $25,000 in 1986.

Research and development, including trials, for new drugs can take up to twelve years. With the help of the NIH, Wellcome managed to carry out this work for AZT in eighteen months. In 1986, a twelve centre trial study began to test AZT for effectivity in AIDS cases. This was the first time that the drug had been used on human beings.

These Phase II trials were terminated prematurely, after a period of only nine months when it was found that while only one of the AZT-taking group had died there were 19 deaths in the placebo group. Many theories have been put forward since, as to why this might have happened. The trial was so badly organised that no follow-up information was recorded on any of the trial subjects, making it impossible to see what might have happened in the longer term.

In 1992, John Lauritsen, an American researcher and writer, obtained documents, under the Freedom of Information Act, from the US Food and Drug Administration (FDA). These documents, although heavily censored, revealed that the trials had become unblinded, with trial subjects crossing between groups; that serious adverse reactions to the drug had gone unreported, including 19 cases of anaemia requiring life-saving transfusions, and that trial records had been altered to reflect better results for the drug. The trial was so chaotic at its Boston centre that in January 1987, the FDA was forced to hold a special meeting to decide whether or not to allow through the data from this and two other centres -- which it did.

After almost four years of licensed use, it was accepted that AZT had a 1,000 times higher toxicity than had been quoted by Burroughs Wellcome in the Data Sheet Compendium or cited in the Physicians Desk Reference in 1986. At an end cost of £10,000 per patient per year, Wellcome attempted to keep the dosage as high as possible. By 1993, however, dosages per day had been reduced by most doctors from 1,200 mg to 500mg (Walker 1997)

In 1990, Wellcome managed to open an expanding market when they got the FDA to license the use of AZT for healthy individuals who tested antibody positive. It was only a short step from this decision to the free dispensing of AZT as a prophylactic -- for example for doctors or nurses who had received needle stick injuries. **Understandably there was immense pressure on FDA to approve AZT even more quickly than they had approved thalidomide in the mid-60s, which ended up causing drastic birth defects.**

At the Ninth International Conference on AIDS, in Berlin, the famous Concorde study (British MRC and its French equivalent) drove a stake through the heart of seemingly endless AZT mythology that had enveloped and governed the AIDS treatment debate for six years. The team had concluded that AZT – a highly toxic and carcinogenic drug – neither prolongs life nor staves off symptoms of AIDS in people who are HIV – antibody positive but still healthy. This had been in literature for many years. A study published in the Lancet had found AZT to be too toxic for most people to tolerate, had no lasting effect on HIV blood levels, and left the patients with fewer CD 4 cells than they had started with (Farber, 1993)

Chapter 5

Useful poisons

There is no fundamental difference between medicinal and poisonous plants. All medicines are useful poisons. The only thing that distinguishes them is the amount taken.

'Dosis sola facit veneum' (Paracelsus 1493-1541)

The following box shows that ART is a package of commodities.

Box 1. Essential medicines and commodities that support the HIV/AIDS programme

Antiretroviral Therapy, ART

The following are factors that should be taken into consideration when choosing ART regimens at both the programme level and the level of the individual patient; drug potency; side-effect profile; laboratory monitoring requirements; potential for maintenance of future treatment options; anticipated patient adherence; coexistent conditions such as TB; pregnancy or the risk thereof; potential drug-drug or drug-nutrient interactions; prior exposure to ARVs and very importantly, availability and cost.

Palliative Care Medicines

This refers to medicines that really do not require specialist attention and can be used at home by the patient. The medicines include such essential drugs as anti-infective agents, antiseptics, pain killers (with controlled access to opiods), antidiarrhoeal agents, cancer drugs and so on. Palliative care can promote ARV adherence.

Treatment medicines

These are medicines to treat tuberculosis, sexually transmitted infections that may present together with HIV infection.

Laboratory investigations

HIV infection requires test kits, CD4 tests, Viral load tests, Full Blood Counts, Liver Function Tests etc.

Prevention

The treatment programme has to be supported by Evidence Based Prevention Programme which requires supplies such as condoms, lubricants, gloves, disposable syringes and needles etc.

Pregnancy & Family Planning

Potential for pregnancy should be taken into consideration when deciding which medicines to avail in the programme. For example efavirenz and nevirapine may interact with oestrogen-based contraceptive.

As indicated in the box, a complete HIV/AIDS programme cannot be successful without essential drugs which have to be available to ensure continuation of care and palliative care. Some of these are over-the-counter drugs or homeopathic treatments / herbal supplements that may interact with ARVs. Just because herbal medicine are natural, it does not mean they are safe. Plants are chemical factories and drugs are chemicals and therefore herbal products will be dealt with by the body or affect the body in the same way as any other chemical. It therefore means that herbal products can interact with pharmaceutical products.

Drug-drug interaction may be harmful or beneficial and not all interactions are of clinical importance and they may not occur in every patient. Constant vigilance is, therefore, required to avoid drug interactions and to spot them when they do occur.

Most people living with HIV/AIDS will experience weight loss at some point in time. There is a relationship between loss of weight or lean body mass and mortality in HIV patients. In order to

prevent weight loss or maintain weight, fight infection, build and maintain muscle mass, it is important to have enough nutrient intake at all times. Sometimes some of these nutrients can interact with drugs being taken, ***drug-nutrient interaction***. Nutrient in the food, for example, fat in the meal increases the level of some drugs in the blood and decrease the level of others. Timing of medications should be adhered to reduce side effects from food-drug interaction.

VARIATION OF ARV – FOOD INTERACTION

* **Some AVs should be taken with food, others on an empty stomach and still others are contra-indicated with certain foods.**
* **Some ARVs reduce nutrient absorption or metabolism and may require food rich in specific nutrients or may require nutritional supplementation**
* **Certain ARVs cause side effects that affect food consumption, and some side effects can be managed by specific food responses.**

Earlier it was indicated that most OIs are due to reactivation of latent organisms in the host and that relapses are common and that continuous suppressive or maintenance treatment is necessary, using drugs that cause side –effects. What are these side effects?

A ***side effect*** is an unwanted effect of drug that is a normal, predictable, dose-related action, occurring at ordinary therapeutic doses: it may be best to confine this term to minor effects and not

to use it as synonymous with ***adverse reaction***: but both terms are often used loosely to include trivial and serious effects.

An adverse drug reaction, ADR, is a harmful or serious unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and / or foretells hazard from the future administration as was the case with *thiacetazone*. This was an anti TB drug which was found to cause severe Stevens-Johnson syndrome in HIV patients.

Starting ARVs is committing to lifelong medication and entails enduring the almost universal initial period of unpleasant side effects. This makes ARVs **USEFUL POISONS.** People who take ARVs and have chronic infection may take breaks, 'Drug Holidays" from treatment for several reasons apart from wanting relief from long side effects. The reasons include:

- Treatment "fatigue' and / or poor adherence
- To stimulate the return of drug –sensitive virus before a change of treatment. This strategy may put people who previously had a low CD4 cell count at risk of illness.
- People who commence ART soon after becoming infected may interrupt therapy in an attempt to stimulate HIV-specific immune responses. This strategy, however, remains unproven.

There are **risks associated** with interruption of ART and these include;

- **Interruption leads to viral rebound and a fall in CD4 count. A previously low CD4 counts puts you at greater risk of a fast and / or significant fall in CD4 cells**

- **CD4 cell decline as indicated earlier may be followed by AIDS-related illness.**
- **A seroconversion-type illness may occur in some people who stop therapy**
- **For treatment experienced people with drug –resistant virus, VL may rise significantly when 'wild type' virus re-emerges.**
- **VL may not be re-suppressed when you restart ART**
- **Resistance may develop or emerge during the drug holiday.**

Chapter 6

Time bomb detonators

When the Concorde study demonstrated the problems with AZT and the first case of HIV AZT resistant was transmitted, the idea of mono-therapy in HIV/AIDS began slowly to lose ground and a lot of data from year to year started coming out resulting in the introduction HAART as a "cocktail". Each class of ARV was expected to attack the HIV virus at a different stage of replication while it is growing in the human lymphocyte cell. The drugs would only be effective as long they were taken religiously to avoid any virologic failure. In other words adherence was emphasized as important in ART right from the outset. Adherence has been defined as the proportion of medications taken divided by the proportion of medication prescribed. For example, if a patient took 45 out of 60 prescribed pills in a 30-day period, measured adherence would be 75%. Generally, adherence is measured on a scale from 0% to 100%. (Descamps et al 2000; Mushlin & Appel ,1977).

Non adherence to ART may lead to the development or emergence of resistance. Drug resistant virus can be transmitted, **in spite of the fact that HIV is a difficult virus to transmit !** This is a fact that a lot of people do not want to accept and deal with it squarely.

Combination ART has markedly improved the prognosis of patients with HIV. Concerns are mounting, however, about a secondary epidemic of drug resistant HIV, the TIME BOMB to be detonated by ARVs. HIV drug resistance - as the province plans to scale up ARV roll out to cater for those in need - is going to render treatment less effective (Eron 2005; Grant et al 2002; Litlle et al 2002). As a matter of fact ARV drug resistance has now been associated with an increase risk of death in patients first starting HAART (Hogg et al, 2005).

Drug resistance to some of the recommended front line drug regimen in South Africa has been demonstrated in the United Kingdom. A cohort study carried out between February 1996 and May 2003 showed that, overall, around 9% of the first line regimen may have had reduced efficacy as a consequence of primary (transmitted) resistance (Dunn, 2005). In the UK , as a result of this study they now recommend resistance testing before therapy as a standard clinical investigation.

Phylogenetic (evolution of the different species) studies from different geographical areas have revealed a remarkable genetic diversity among HIV-1 strains with several distinct lineage. Most strains in the global epidemic belong to group M, which include several subtypes , or clades , designated by the letter A to K. In addition, nearly 20% of group M isolates are recombinants, with genetic material originating from different subtypes. Overall, the predominant viral clades are A and C, which account for one-half of the infections and B, the major subtype in USA and Europe.

The greatest diversity in HIV-1 is in Africa, where all subtypes and groups are found. Due to global travel and migration, wider geographic dissemination of all HIV-1 subtypes is expected in the future, as well as the emergence of an increasing number of recombinant variants.

Most information on ARV drug efficacy, and most existing data on resistance, has been collected for group M, subtype B virus, which is the most prevalent type in the USA and Europe.

What is already known about HIV drug resistance in Limpopo?

- Primary HIV drug resistance limits therapeutic options
- Its spread will have a negative impact on the expected reductions the number of people dying and suffering from HIV/AIDS.
- We have no clue in the province on the level and pattern of drug resistance

A study by Lukhuleni, Jali, Maputle and Mothiba (Nursing Sc) will hopefully shed some light on the level of AART adherence

What is needed now as ART is being scaled up in the province, is a provincial HIV Drug Resistance, HIVDR, Plan in order to develop HIVDR Early Warning Indicators which include;

- **Drug stockouts at ART sites**
- **Prescribing practices**
- **Continuation of 1st line drugs**
- **Appointment keeping**
- **Drug pickup**

Chapter 7

Conclusion

In conclusion, generally speaking any pharmaceutical product has the following latent functions:

- Power to heal
- Power of the modern technology
- Identification that a situation is legitimately medical
- Legitimizes sick role status
- Socio-Politico-economic tool and, ARVs are not exceptions.

ARVs have created false hope of safety among users. Treatment failure is going to be common if people do not change their risk behaviour, by taming their sexual hormones!

It is biologically plausible that effective use of ARVs would reduce viral loads in vaginal fluids and semen – and as result reduce sexual transmission. It is also plausible that the HIVDR can still be transmitted in the vaginal and seminal fluids if the drugs are misused.

Continuous drug information or even drug counseling and education for communities and society on the realities of HIV drugs should be in place before scaling up ART roll out. ARVS are neither a cure nor a preventive tool per se.

I hope I have let the little I have learnt about HIV/AIDS go forth into the day in order that someone better than I may guess the truth about HIV and the drugs used. And his / her work may prove and rebuke my error or errors. At this I shall

be very happy that I was yet a means where by the truth about HIV / AIDS has come to light.

Chapter 8

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CITATION

Professor Norman Zimunda Nyazema holds a BSc (Life Sc) , BSc (Pharmacology) and PhD from the "red brick" University of Liverpool, UK. Soon after graduating in 1981 he went back to Zimbabwe and joined the Department of Clinical Pharmacology, Godfrey Huggins Medical, at the University of Zimbabwe. He was the Chairman of the Department, 1984 – 1989 and Director, Postgraduate Studies Department, 1991 – 2002. He has been a member of staff there for more than 20 years before joining UNIN now University of Limpopo, School of Health Sciences. He continues to have research collaborating with his former colleagues at UZ while teaching at University of Limpopo.

He has no purist approach to research in health and medical sciences where he has published many papers and continues to do so. His research are in Health Systems, Ethno-pharmacology, Pharmaco-epidemiology, Immuno-pharmacology. Because of his interest in nutritional pharmacology, he is a board member of Nestle Nutrition Institute in Africa. This is a body set up by Nestle to promote research in nutrition in Africa.

Prof Nyazema also belongs to a consortium of researchers in South Africa, the Novel Drug Platform, that is looking at development of pharmaceutical products utilizing Indigenous Knowledge. He represents the University of Limpopo.

He is currently a WHO consultant in Regulatory Pharmacology, Procurement, Supply, Management and Use of HIV/AIDS and Essential Drugs.