# TLALELETSO

## New Antiretrovirals

*What's new in HIV treatment?*

In this issue of Tlaleletso we review what new drugs are in the pipeline for treating HIV - both for Botswana and other countries.

# INTRODUCTION

Over the last twenty years there has been an incredible amount of research to develop effective drugs to treat HIV. There are now more than twenty antiretroviral drugs available worldwide, although currently only some of them (11) are available in Botswana. In this edition of Tlaleletso we review currently available ARVs as well as new drugs in the pipeline.

# FIRST LINE

In Botswana clinicians have a choice of several different drugs that they can prescribe patients that need to start Highly Active Antiretroviral Therapy. Most patients that have not been on antiretrovirals (ARVs) before are initiated on a fixed dose combination of tenofovir, emtricitabine and efavirenz, (Atripla). An alternative, nevirapine is recommended when patients are intolerant of efavirenz. Nevirapine is prescibed in combination with tenofovir and emtricitabine (Truvada) or Zidovudine and 3TC (Combivir). The side effects of these drugs are outlined at the end of this issue of Tlaleletso.

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## Notes from the Editor…..

Tlaleletso is a monthly publication produced by the Botswana UPenn Partnership, in response to your expressed need for accessible, digestible clinical information.

In this issue we focus on HIV treatment and what drugs are available, both in Botswana and elsewhere

DID YOU KNOW?

AZT was the first drug to be made available for the treatment of HIV in 1987. It was also the fastest ever drug to pass from research and development into clinical use in the US (25 months).

# SECOND LINE

The standard second line regimen for those patients that have failed tenofovir, emtricitabine and efavirenz includes zidovudine, lamivudine (combivir) and lopinavir/ritonavir (Aluvia). Under certain circumstances abacavir may be used as part of a second line regimen. It is vital that all patients failing first line drugs and initiated on second line regimens receive *intensive* adherence support, to ensure that the efficacy of these second line drugs is not compromised as well.

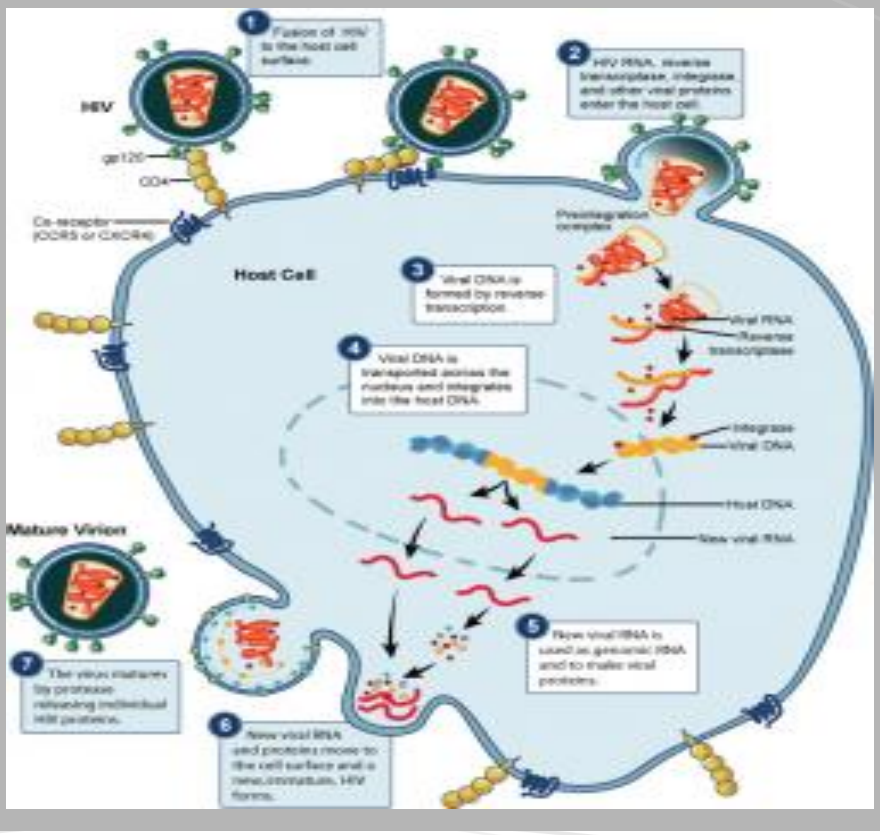
# THIRD LINE

If patients do fail these regimens and HIV develops mutations to first line drug and second line regimens, there is limited availability of specific third line regimens. Before initiating these drugs extensive adherence counseling is always necessary. Third line drugs are only prescribed by specialists working at Princess Marina. Therefore all patients in virologic failure on second line drugs should be referred to the failure clinic at PMH. If patients are intolerant of alluvia ( because of uncontrollable nausea, vomiting, diarrhea or changes in taste) atazanavir/ritonavir may be considered. Atazanvir is only available PMH.

## WHAT'S NEW?

There are many different drugs that are currently being developed by pharmaceutical countries around the world. However, before drugs can be prescribed to patients a huge amount of research has to be undertaken to make sure that the drugs work, that they are safe and that they do not interact adversely with other drugs. All drugs must pass through a series of research trials and be proven to be efficacious before they are made available to doctors.

## HIV REPLICATION CYCLE



# ARVs: what's in the pipeline?

Improved understanding of the life cycle of HIV has allowed for the development of six currently available classes of antiretroviral therapy. Each of these different classes of drugs acts at one of these steps in the HIV life cycle (see diagram on page 2) to inhibit the virus from propagating. In brief, each of these drug classes is described below, as are examples of new drugs under development:

## NNRTIs

NNRTIs (non-nucleoside reverse transcriptase inhibitors) are an older class of antiretroviral drug – the first was approved in 1996. NNRTIs stop HIV replicating within cells by interfering with HIV's reverse transcriptase protein which it needs to make new copies of itself. In Botswana only two members of this group are available: efavirenz and nevirapine (both widely used in first-line treatment). Another NNRTI, delavirdine, has been around for sometime but is rarely used. Because these three drugs work in a very similar way, once HIV develops resistance to one of them then the others are often ineffective as well. Newer NNRTIs are designed to work differently so as to avoid this problem of cross-resistance.

**Etravirine:** One exciting example of a newer NNRTI is called etravirine. While not available in Botswana, it is available in Europe and North America. It is active against some strains of HIV that are resistant to nevirapine and efavirenz. Like older NNRTIs it is associated with potentially life threatening skin reactions. Despite Etravirine not being available here in Botswana it might one day be approved by NASCOD. For this reason it is absolutely necessary to switch patients from efavirenz or nevirapine if they are failing treatment in spite of intensive adherence counseling support. Leaving a patient on either Efavirenz or Nevirapine when they have resistance will eventually lead to resistance to Etravirine as well. This is in turn might have implications for future regimens if and when they become available here in Botswana.

**Rilpivirine:** This drug was approved in the US in 2011. It is a once-daily pill to be taken in combination with other drugs, as part of first-line treatment for treatment-naive patients (those who have never taken antiretroviral therapy before). In the trials, rilpivirine (also known as Edurant) was proven to be as effective in lowering viral load as efavirenz, but fewer patients stopped the treatment due to side effects (Cohen, Lancet, 2011). However, unlike with efavirenz, viral load at the beginning of treatment was found to impact the effectiveness of ripivirine. Like efavirenz, rilpivirine is being prescribed in combination with tenofovir and emtricitabine, as a once a day pill.

**Failure clinic at PMH**

If you think your patient may be failing second line therapy and warrant evaluation for third line ARVs consider referring them to the ***Wednesday HIV Failure Clinic*** at Princess Marina. Alternatively call Miriam Haverkamp for-over-the-phone advice: +267 76 516 520

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# ARVs: what's in the pipeline?

## NRTIs

NRTIs (nucleoside/nucleotide reverse transcriptase inhibitors) were the first medicines to be approved for the treatment of HIV. NRTIs stop HIV from replicating within cells by inhibiting the reverse transcriptase protein. Six of these drugs are currently available in Botswana. Typically an antiretroviral treatment combination consists of two NRTIs and one drug from another class.

Examples of NRTIs that are currently being researched include Apricitabine, Elvucitabine and Racivir. Apricitabine and Racivir are similar in structure to lamivudine and emtricitabine, which are widely used in first-line treatment. Preliminary data suggest that all three of these experimental drugs can control HIV that is resistant to some other NRTIs, so they may provide useful options for second-line treatment.

## Protease Inhibitors (PI)

Protease inhibitors have been available for the last 15 years. In Botswana the most frequently prescribed PI is the combination drug, Aluvia, which is a fixed dose combination of lopinavir and ritonavir. Darunavir is another example of a PI. It is available in Botswana for those patients that have failed first and second line agents.

**Atazanavir:** As mentioned earlier, in cases of intolerance to Aluvia Atazanavir is available here in Botswana through the resistance clinic at PMH. It was approved for use in the US in 2003. It is a once-daily dose of 400mg when unboosted or 300mg when co-administered with ritonavir 100mg. It is well tolerated and in contrast to other PIs has little effect on cholesterol and triglyceride levels.

**CHECK OUT THE GUIDELINES!**

More detail on what drugs are available and what should be prescribed and when are available in the Botswana HIV and AIDS Treatment Guidelines, published in 2012.

Unconjugated hyperbilirubinemia is a common and reversible adverse effect, which occurs in most patients but generally does not require treatment discontinuation. Unless the AST and ALT rise on Atazanavir or he patients has symptoms there is no need to stop the treatment.

Importantly, this drug should not be prescribed with drugs that severely reduce gastric acid secretion (such as omeprazole). In the case of gastritis one can give Ranitidine or Cimetidine but the Atazanaivr should be given at least 10 hours before or after the H2 blocker. In addition, Atazanavir cannot be given to patients on TB treatment as it might cause severe liver damage.

## Integrase inhibitors (II)

Integrase is an enzyme produced by HIV. This chemical performs a crucial role in an early stage of HIV's replication process, which takes place inside human cells. Integrase inhibitors block the action of this enzyme, thus preventing the virus from making new copies of itself against HIV that has become resistant to other antiretroviral classes.

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**Raltegravir** – This drug was first available in the US in 2007. It is notable for the speed with which it suppresses HIV. So far no serious side effects have been observed. Raltegravir tablets are taken twice daily. Recent case reports involving patients taking raltegravir and unboosted atazanavir twice daily suggest this combination may be an option for patients intolerant of ritonavir

## Entry inhibitors

In order to enter a human cell, HIV must first attach itself to proteins on the cell's surface. The virus always begins by latching on to a protein called CD4. The next stage involves proteins called co-receptors, of which there are two main types: CCR5 and CXCR4. Some strains of HIV use CCR5, others use CXCR4, and some can use either.

CCR5 antagonists are a type of entry inhibitor that bind to the CCR5 co-receptor so that HIV cannot exploit it to gain entry to a cell. The main drawback of these drugs is that they don't work against all strains of HIV.

Most people newly infected with HIV carry strains that only use the CCR5 co-receptor. As time passes the virus tends to diversify, so that around half of people in the more advanced stages of HIV infection have strains that can use CXCR4. So-called tropism tests can distinguish between the two types of virus, but these sometimes fail to detect low levels of the CXCR4-using strains.

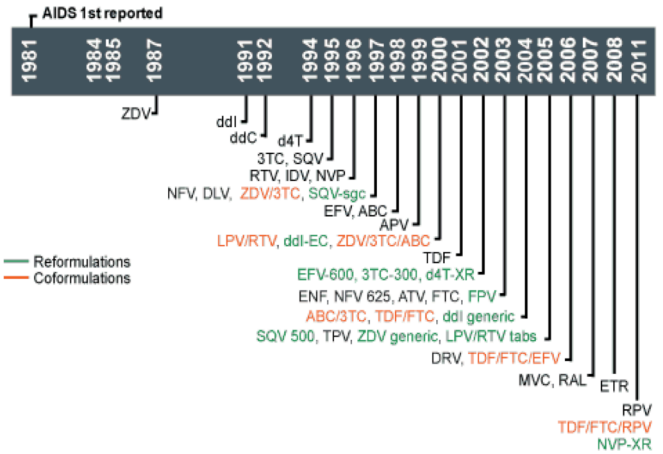
**Maraviroc** became the first CCR5 antagonist to gain approval in the US in2007. This drug – marketed as Selzentry in the US and Celsentri in Europe – comes as tablets to be taken twice per day. In Europe, Maraviroc is only approved for use in patients who have exhausted other treatment options, but in the US its use in first-line therapy. Given that it is necessary to perform an expensive blood test –a tropism test – to confirm that it will even work in each individual patient, it is unlikely that it will become available in the public sector in Botswana at any point in the near future.

## Fusion Inhibitors

Enfuviritide was the first of a novel class of ARVs used in combination therapy for the treatment HIV-1 infection.

Enfuvirtide therapy costs an estimated US$25,000 per year in the United States. Its cost and inconvenient dosing regimen are factors behind its use as a reserve, for "salvage" therapy in patients with multi-drug resistant HIV. It is not available in Africa.

**Timeline of HIV drugs (**image courtesy of clinical care options)




*3TC, lamivudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; DLV, delavirdine; DRV, darunavir; EFV, efavirenz, ENF, enfuvirtide; ETR, etravirine; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; LPV, lopinavir; MVC, maraviroc; NFV, nelfinavir; RTV, ritonavir; RAL, raltegravir; RPV, rilpivirine, SQV, saquinavir; TDF, tenofovir; ZDV, zidovudine.*

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## CONCLUSION

The availability of multiple agents from across these classes of antiretrovirals has made virologic suppression possible for nearly all adherent patients. There have been significant improvements in pill burden, dosing schedules, and tolerability in antiretroviral therapy regimens.

With the development of Dolutegravir, a new example of integrase inhibitor, and its performance in recent trials (no resistance observed during trial) many specialists think that the development of HIV drugs will stop or slow down significantly in the coming years. This will make the treatment choices for patients here in Botswana, who develop resistance on the currently available regimens, in the future limited. This fact emphasizes how important it is to assure good adherence and to manage patients with virological failure pro-actively.

While not all of these drugs are currently available in Botswana, clinicians should remain up-to-date regarding drug-drug interactions and the toxicity profiles of newer medications as they become available.

## Upcoming Lectures

**February**
HIV update: new drugs

**March**
Complicated cases: Diabetes

**April**
HIV update: IRIS

**May**
Infection Control

Got a clinical question about a complicated medical patient or a patient with HIV?

**Mike Reid**
267 724 78 777
**OR**
**Miriam Haverkamp**
267 76516520

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# ARV Side effects & Contraindications

| Drug | Contraindications | Toxicity/incidence | Risk Factors |
|---|---|---|---|
| AZT (zidovudine) | Severe anemia | Anemia (up to 45%)<br>Cytopenias when used with rituximab/CHOP<br>Myopathy.<br>lactic acidosis<br>GI intolerance (up to 50%), hepatic steatosis<br>Increased MCV<br>Mucosal pigmentation | Existing anemia (Hgb <9.5)<br>Female gender<br>Lower CD4 counts |
| 3TC/FTC (lamivudine/emtricitabine) | | Slightly higher incidence of skin discoloration in clinical trials with FTC. Lactic acidosis rare<br>Rash up to 10% with 3TC. Pancreatitis 0.3% | |
| TDF (tenofovir) | Renal failure | Renal failure from proximal tubular acidosis and Fanconi Syndrome, metabolic acidosis, diabetes insipidus, acute tubular necrosis.<br>Decreased bone density<br>Bone demineralization in infants (congenital abnormality risk 2.3%--similar to other ARVs)[12]<br>Lactic acidosis extremely rare.<br>Rash in up to18% | Underlying renal disease or other risk factors for nephrotoxicity |
| ABC (abacavir) | Previous hypersensitivity reaction | Hypersensitivity reaction in 5-8%<br>Myocardial infarction within first 6 months of use[7] Lactic acidosis extremely rare | HLA-B-5701<br>Female sex |
| DDI | | Pancreatitis, lactic acidosis, peripheral neuropathy, retinal changes and optic neuritis, lipoatrophy | Lipodistrophy risk factors: older age, CD4 nadir<100, BMI<24 |
| D4T | | Pancreatitis, lactic acidosis, peripheral neuropathy, lipoatrophy, dyslipidemia, hepatic steatosis | Lipodistrophy risk factors: older age, CD4 nadir<100, BMI<24 |
| Nevirapine | Initial CD4 count > 250 for women >400 for men<br>Previous life threatening hepatotoxicity or Stevens-Johnson syndrome | Hepatotoxicity<br>Rash up to 18%<br>Stevens-Johnson Syndrome (<1%) | Women>men<br>Pregnancy<br>Coadministration of fluconazole |
| Efavirenz | Pregnancy | CNS effects, gynecomastia<br>Serious psychiatric symptoms | |
| Lopinavir/ritonavir | | Nausea, abdominal bloating, diarrhea, dyslipidemia<br>Hepatotoxicity<br>Insulin resistance | Use of PI with two NRTIs may increase risk of lipoatrophy |