TENOFOVIR: An explanation of why we need TDF-based fixed-dose combinations and the steps to bring them to the market in South A

By *moderator*
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1. MAKING TDF FDCS A 1ST LINE REGIMEN IN THE PUBLIC SECTOR
The majority of patients in South Africa on antiretroviral (ARV) therapy ? most of whom are treated in the public sector ? are on regimens that include stavudine (d4T). While d4T has saved many lives, its use should be phased out because of the associated side effects of the drug. D4T use should be reduced and replaced by tenofovir disoproxil fumarate (TDF), which has a better side-effect profile thus requiring fewer treatment switches.

TDF is now available in some parts of the world as part of a fixed-dose combination (FDC) that makes ARV treatment as simple as taking one pill once a day. Such FDCs are more convenient for patients and are also cheaper for the public health system to procure as well as easier to manage. While d4T is also available as part of a FDC, this combination - which includes lamivudine (3TC) and nevirapine (NVP) ? is less widely used than other regimens.

In the public sector, TDF is available ? to a limited extent ? to patients who experience toxicity or resistance. In part, this is because of the relatively high cost of TDF in South Africa as a result of a lack of competition. While TDF is not under patent protection in South Africa, there is currently only one product available on the market: co-branded by Gilead Life Sciences and Aspen Pharmacare as Viread. FDCs containing TDF are not yet available.

All the evidence points to the need for the first-line public sector regimen to include a TDF-containing FDC, such as the combination of TDF, emtricitabine (FTC) and efavirenz (EFV) or TDF, lamivudine (3TC) and EFV. The branded version of the first combination ? Atripla ? is currently awaiting registration by the Medicines Control Council (MCC). To date, no generic versions of the drug have been submitted to the MCC for registration, nor have any versions of TDF/3TC/EFV.

To secure access to TDF as part of a first-line regimen, the following steps should be taken:

1. The 2010 upcoming tender must include special provisions for drugs not yet registered in South Africa that have already been approved by an international regulatory body such as the US Food and Drug Admininstration (FDA).
2. Generic companies need to submit their dossiers for TDF and TDF-containing FDCs to the MCC for registration;
3. The MCC must fast-track the registration of all TDF products, including TDF-containing FDCs;
4. The Department of Health (DoH) must commit to procuring FDCs where available;
5. The ARV treatment guidelines must be updated to include TDF as part of standard first-line regimens, with a preference for TDF-based FDCs.

2. CLINICAL ADVANTAGES OF TDF
Clinical trials have shown the advantages of TDF over d4T. A study presented at the International AIDS Society Conference 2009 in Cape Town showed that d4T-containing regimens have more serious side effects and require more drug switches than regimens containing TDF. The study compared 1000 patients from Zambia on a regimen of TDF-

FTC-NVP with 1000 patients from South Africa on a regimen of d4T-3TC-NVP. The result compared the effects of d4T vs TDF. NVP was consistent in both regimens and FTC and 3TC are clinically interchangeable. The results showed that in the d4T scenario, 50.5% of patients experienced a d4T-related toxicity and 16.2% were switched to a new drug by the end of 2 years. In Zambia only 2.5% of patients experienced a TDF-related toxicity and were switched to AZT.

Serious side effects that are associated with d4T include lactic acidosis, lipodystrophy, peripheral neuropathy and pancreatitis. In contrast, patients on TDF experience far fewer serious side effects. While TDF is associated with a slightly increased risk of renal (kidney) toxicity, this can be monitored by checking creatinine levels. In addition, studies have shown that damage done to the kidneys is usually reversible with drug withdrawal. TDF can also have a small effect on bone toxicity in the first year of treatment. This too should be monitored.

3. CONVENIENCE AND IMPROVED ADHERENCE OF FDCs

FDCs, which combine all the drugs in a particular regimen into a single pill, are preferable for patients because they are simpler to take and thus more convenient. FDCs have also been recommended by health professionals and the Southern Africa HIV Clinicians Society because the lower pill burden is associated with improved adherence.

The improved adherence associated with a lower pill burden has been established through a number of studies that have tracked adherence. An analysis of nine studies tracked the adherence of 20,242 patients - 11,925 patients on fixed-dose combinations and 8,317 patients on free-drug combination regimens (multiple drug regimens) - over an average of 8.6 months. The analysis showed that the risk of non-compliance is reduced by 26% [95% CI, P <.0001] for patients on FDCs.

Poor adherence of antiretroviral therapy is associated with increased treatment resistance. Second and subsequent line regimens still remain far more expensive than first line regimens. Therefore in the long term FDCs could represent a cost savings because of a decreased need for more expensive 2nd line treatments. Purchasing FDCs will also simplify supply chain management for the DoH.

Globally, the following TDF-based combinations are available:

- TDF/3TC;
- TDF/FTC;
- TDF/3TC/EFV; and
- TDF/FTC/EFV.

As well as FDCs, TDF-based regimens are also available in co-packs, i.e. TDF as a single pill or a double FDC (such as TDF/FTC, which is marketed in South Africa as Truvada) co-packaged in a blister with the remaining ARVs in the regimen. For example, Truvada is usually taken with a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as EFV or NVP. A co-pack would therefore include TDF/FTC with the NNRTI in the same blister.

4. PRICING OF TENOFOVIR

The availability of TDF in the public sector has generally been limited by the high costs of the drug. However following an agreement with the Clinton Foundation HIV/AIDS Initiative (CHAI), Matrix Laboratories ? an Indian-based generics manufacturer ? has committed to market TDF-based FDCs at prices that are competitive with South Africa?s first line d4T-based regimens.

TDF-based FDCs marketed through the CHAI agreement are less than the cost of the most commonly used first line regimen of d4T + 3TC + EFV. While the cost are still slightly higher than the cost of first line regimen containing d4T + 3TC + NVP, less than 30% of patients are on this regimen.

Cost per patient per month of first line-regimens in the public sector
d4T + 3TC + EFV R163.49 (US$22)

d4T + 3TC + NVP R82.16 (US$11)

Cost of TDF-containing FDCs procured through CHAI
* These prices do not include the costs of transport or import tax. The mark up has been estimated at around 29%.
TDF/ 3TC/ EFV R132 (US$17.50)
TDF/ FTC/ EFV R151 (US$19.92)

In terms of the CHAI agreement, lower prices are available to members of the procurement consortium but are dependant on volumes ordered. South Africa is not currently a member of the CHAI Procurement Consortium. However it is clear from this deal that if TDF-based FDCs are produced at sufficient volumes then they can produced and marketed at prices that are competitive with d4T regimes. South Africa has the largest ARV tender in the world and therefore would certainly meet the volumes required by generic companies to produce and market TDF-based FDCs at competitive prices.

5. LICENCES AND TENDERS
In order to bring TDF-based FDCs to the market, and in particular to participate in the public sector tender, a generics company will not only have to register its products in South Africa but also ensure that it is not infringing on whatever patents may exist in respect of each ARV drug in the relevant combination.

For example, the 2008 ARV tender specifications include the following condition: ?Bidders must submit a copy of the actual patent or an agreement with the patent holder.? This clause should be removed or amended to reflect the fact that permission to bring generics to market is not always granted in terms of express licensing agreements. Some patent holders simply choose not to enforce their exclusive rights in South Africa.

What is the patent and licensing status of the relevant ARVs in the TDF-containing FDCs?

? The patent for TDF is held by the pharmaceutical company Gilead. In South Africa, Aspen Pharmacare markets the drug under the brand name Viread. This is done in terms of an exclusive marketing and distribution agreement. Importantly, however, TDF is not under patent in South Africa, meaning that there is no need to obtain Gilead?s permission to bring generic versions of TDF to market.

? The patent for 3TC is held by Biochem Pharma, a Canadian-based company that granted GlaxoSmithKline (GSK) an exclusive licence to market the drug globally. Following a complaint filed by the AIDS Law Project (ALP) on behalf of Hazel Tau and others with the Competition Commission in 2002, a number of locally-based generics companies were licensed. Generics companies in South Africa that hold a license to market 3TC include Cipla-Medpro, Adcock Ingram, Sonke Pharmaceuticals and Aspen Pharmacare. The main patent on 3TC in South Africa expires in February 2010.

? The patent for FTC in South Africa is held by Emory University, a US university that granted Triangle Pharmaceuticals an exclusive licence to market the drug globally. Gilead Sciences acquired Triangle Pharmaceutical and now holds the license for FTC. The FTC patent is not enforced in South Africa.

? The patent for EFV in South Africa is held by MSD. Following a complaint filed by the ALP on behalf of TAC with the Competition Commission in 2007, MSD licensed a number of locally-based generics companies and amended the terms of its two existing licensing agreements. Generics companies in South Africa that hold a license to market EFV include Aspen Pharmacare, Aurobindo, Cipla-Medpro, Sonke Pharmaceuticals and Adcock Ingram.

At this point we can confirm that there are no patent barriers in the way of Aspen Pharmacare, Sonke Pharmaceuticals, Cipla-Medpro and Adcock-Ingram to market all the TDF-containing FDCs in South Africa. As of February 2010, when the main 3TC patent expires, this list will also include Aurobindo. It is important to note that in terms of an exclusive supply agreement, Aspen has access to the full range of Matrix ARV products, including both TDF-containing 3-in-1 FDCs.

6. REGISTERING FDCs WITH THE MCC

For many years, the MCC has failed to ensure that South Africans are able to take advantage of scientific advances for the treatment and prevention of HIV. Slow registration of drugs has prevented new and better drugs from entering the market. For instance, TDF was approved by the FDA in October 2001, but it was only approved by the MCC in April 2007. While some of the blame for this late registration must be borne by Gilead and Aspen, delays at the MCC were also responsible.

The MCC must be strengthened and given the necessary resources to ensure that new and better drugs of proven quality, safety and efficacy are registered efficiently. These include paediatric formulations and FDCs. In particular, the registration of TDF-based FDCs must be fast-tracked to allow them to be procured in the 2010 ARV tender. The law currently makes provision for this to happen.

Importantly, the MCC is focused on clearing its registration backlog. The efforts to improve the drug registration process are based on the 2009 report of the Medical Products Technical Task Team, which was set up by former Minister of Health Barbara Hogan. Under the guidance of the Minister Aoron Motsoaledi, plans are also underway to strengthen the MCC and to transition to a new independent and accountable drug regulatory authority.

7. PROVISIONS TO BE INCLUDED IN THE 2010 ARV TENDER

The current antiretroviral tender runs from June 2008 through May 2010. Because there are still no generic TDF FDCs registered with the MCC the upcoming tender must include provisions to allow for TDF FDCs to be purchased in the next tender without MCC registration. Drugs that are not yet registered with the MCC must already be registered or have tentative approval from another stringent regulatory body such as the FDA. These drugs must be fast-tracked for registration with the MCC.

Matrix?s TDF-based FDCs have already secured tentative approval from the FDA. The FDA grants tentative approval to generic versions of products that are still under patent. Once the patents expired, this automatically becomes full marketing approval.

8. UPDATING TREATMENT GUIDELINES

Treatment guidelines should be updated to clearly define the product use of TDF-based FDCs in first-line regimens. The National Health Council must approve changes to the treatment guidelines. The National Health Council acts on the recommendations of the National Essential Drug List (EDL) Committee on the range and types of products to be used for the treatment of HIV-positive patients. The South African National AIDS Council can also make recommendations on updating the treatment guidelines in order to improve prevention, treatment and care of HIV/AIDS.

9. CONCLUSION

TDF-based regimens are now being sold at prices that are competitive with d4T-based regimens. If accessed, these competitive prices will allow the DoH to improve regimens without the need for additional financial resources. The steps laid out above must be taken to ensure that these competitive prices are available in South Africa, so that first line d4T-based regimens can be phased out and replaced with TDF-based FDCs.

10. GLOSSARY

MEDICINES CONTROL COUNCIL

The Medicines Control Council (MCC) is a statuory body established under the Medicines and Related Substances Act 101 of 1965 that controls how medicines are developed, registered and used in South Africa.

THE NATIONAL ESSENTIAL DRUG LIST COMMITTEE

The National Essential Drug List Committee is a body required by the National Drug Policy. The committee is made up of a number of medical specialists, a member of the clinical committee of the Medicines Control Council, a health professional involved in drug management training and representatives of the provincial essential drug list committees. Members of the committee are appointed by the Minister of Health and responsible for the selection of drugs to be used in the public sector.

NATIONAL HEALTH COUNCIL

The National Health Council was established under the National Health Act 2003 (Act No 61 of 2003). The National Health Council is an advisory body to the Health Minister made up of government officials. The National Health Council may consult civil society to advise on health policy.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR

A member of a class of compounds, including Nevirapine and Efavirenz, that acts to directly combine with and block the action of HIV?s reverse transcriptase enzyme. NNRTI block the process of RNA converting into DNA and make it difficult for HIV to multiply.

SOUTH AFRICAN NATIONAL AIDS COUNCIL

The South African National AIDS Council (SANAC) is a national body established to oversee and advise government on HIV and AIDS in South Africa. SANAC was formed to strengthen the strong political leadership as well as to ensure inclusion of civil society in the overall response to HIV and AIDS. The Council is composed of both government and civil society organisations.

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