



ADVICE DOCUMENT

Fixed-dose combination for adults accessing antiretroviral therapy

Southern African HIV Clinicians Society

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This document serves to guide clinicians and programme managers on how to switch from 3 separate antiretroviral (ARV) drugs to the new, single, fixed-dose combination (FDC) tablet containing tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV).

Summary

Transitioning from individual drugs to an FDC tablet needs to be managed carefully, particularly regarding stock management, ordering processes, supply-chain integrity and comprehensive patient counselling.

Priority groups

- Initially, FDC supply will be insufficient to provide for all FDC-suitable patients
- Therefore, the National Department of Health (NDoH) has recommended that the following patient groups be prioritised for FDC initiation/switch:
 - Priority group 1:** All HIV-positive patients newly initiating ART – adults, adolescents and pregnant women (regardless of CD4 count (amendment to the guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) anticipated in April 2013) – and who do not have contra-indications to the FDC component drugs
 - Priority group 2:** HIV-positive pregnant women **and** breastfeeding mothers currently stable on lamivudine (3TC), TDF and EFV
 - Priority group 3:** Virologically suppressed patients on a stavudine (d4T)-based regimen and who have normal renal function
 - Priority group 4:** Stable patients receiving individual TDF, 3TC and EFV and who have tuberculosis (TB) co-infection
 - Priority group 5:** Stable patients receiving individual TDF, 3TC and EFV and who have other co-morbidities (e.g. hypertension, diabetes)
 - Priority group 6:** Patients receiving individual TDF, 3TC and EFV and who request to switch to the FDC treatment
 - Priority group 7:** Patients receiving individual TDF, 3TC and EFV and who, after counselling, agree to switch to the FDC treatment.

Important: Clinic staff must co-ordinate this process and only switch as many patients to the FDC tablet as stock allows. This should avoid patients being switched back and forth between FDC and individual drugs due to insufficient stock.

Note: The FDC tablet is not significantly larger than EFV or lopinavir/ritonavir (LOP/r) (Aluvia); therefore, swallowing should not be problematic.

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In 2012 Dr Aaron Motsoaledi, South Africa (SA)'s Minister of Health, announced the award of a new antiretroviral (ARV) tender – worth R5.9 billion – that, for the first time since the start of the ARV programme, includes a triple fixed-dose combination (FDC) tablet. The FDC tablet will contain 300 mg tenofovir (TDF), 200 mg emtricitabine (FTC) and 600 mg efavirenz (EFV). This is a significant step forward for SA's national ARV programme, as it enhances cost-effectiveness and simplifies the first-line regimen. It is anticipated that over 90% of new patients will be eligible to initiate this FDC treatment.

Advantages of FDCs Regimen and stock management simplification

- ARV prescribing, dispensing and stock management is simplified because the first-line regimen is reduced from 3 separate drugs to 1 combined tablet.^[1]

- From April 2013, all pregnant women, regardless of CD4 cell count, will be initiated on triple ARV therapy for the duration of pregnancy and breastfeeding, to enhance the prevention of mother-to-child transmission of HIV (PMTCT) programme. The FDC tablet will simplify the rollout of this change.

Adherence

- Reducing the pill burden of the first-line regimen to 1 pill once daily may, as reported in some studies,^[2-4] improve adherence levels. However, the provision of intensive adherence counselling remains essential.

Efficacy

- The efficacy of TDF/FTC/EFV-based triple ARV therapy has been proven in randomised controlled trials.^[5-7]

Guaranteed dosing and consistent dispensing

- There is a decreased risk of incorrect dosing due to patient misunderstanding and/or prescribing/dispensing errors.
- Patients are unable to default single drugs to avoid certain side-effects (e.g. some patients independently discontinue EFV because of dizziness or drowsiness).
- There is a reduced risk of patient exposure to dual therapy during single drug stock-outs.

Cost

The SA Government negotiated a cost of R89.37 per month for the FDC treatment.^[8] This represents significant cost-saving compared with the old, single-drug tender.

Are 3TC and FTC interchangeable?

The majority of patients currently accessing ARVs are prescribed lamivudine (3TC). However, the FDC will contain FTC. FTC and 3TC are structurally very similar, FTC having just one additional fluorine molecule. In a recent technical update, the World Health Organization (WHO) concluded that 3TC and FTC are clinically and programmatically interchangeable.^[9] Although few direct comparisons have been performed, 3TC and FTC appear to have comparable virological and clinical efficacy and safety. 3TC may rarely be associated with pure red-cell aplasia, which requires drug substitution, and FTC may occasionally cause palm discolouration, which is usually managed by reassuring patients. Both drugs are active against the hepatitis B virus. Therefore, WHO concludes that 'FTC is an acceptable alternative to 3TC' and that '3TC may substitute for FTC or *vice versa*'. Both 3TC and FTC are given as a single daily dose. Therefore, for those patients receiving stavudine (d4T), 3TC and EFV, switching to the FDC treatment can be considered as a single drug switch from d4T to TDF because 3TC and FTC are considered to be equivalent.

Supply chain management

It is imperative that all patients enrolled in the SA ARV programme are able to access a continuous supply of ARV treatment. Treatment interruptions, whether of single or multiple ARVs, are associated with poorer clinical outcomes, increased rates of virological failure and the emergence of drug-resistant HIV. Consequently, prescription of the FDC

tablet will need to be managed carefully, particularly in terms of stock management, ordering processes and supply chain integrity. A gradual, phased approach to introducing the FDC treatment to new patients, pregnant patients and those receiving d4T should help to ensure a smooth transition.

District managers, facility managers, healthcare providers and pharmacy staff will need to work closely together to track how many patients are initiated on, or switched to, the FDC treatment, while also monitoring how many existing patients remain on various single drugs. Changes to monthly/quarterly orders must be kept in line with the needs of each facility's patient population. Facility staff will need support to manage the transition and to communicate effectively with the National Department of Health (NDoH) should shortages arise (preferably before complete stock-outs occur). As the proportion of patients on 'non-standard' regimens decreases, it will become increasingly important for facilities to manage their single drug stocks to avoid stock-outs which disadvantage patients who are not eligible for the FDC.

Switching patients to the FDC

SA's FDC producers will need time to maximise production. Considering that previous drug stock-outs arose when demand outstripped the manufacturers' capacity, it is imperative that FDC rollout is undertaken in a carefully controlled, phased approach. Under the January 2013 - December 2014 ARV tender, 30 million units of FDC will be produced for nationwide use. Due to the size of SA's ARV programme, this means that FDC provision will have to be limited to specific patient groups. Based on the existing tender, the NDoH has identified the following groups as eligible for FDC use. Currently, the Southern African HIV Clinicians Society recommends that clinicians adhere to these NDoH guidelines, to avoid FDC stock-outs occurring as a result of clinics over-extending beyond the anticipated maximum FDC availability during the current tender.

Priority patient groups (NDoH recommendations)

Priority group 1: All ARV-naive patients newly initiating ART

- All HIV-infected individuals identified as eligible for ART, including those with

tuberculosis (TB) co-infection, should be initiated on the FDC treatment as long as there are no contra-indications to the component drugs (e.g. renal dysfunction precludes TDF use, and a recent psychotic episode precludes EFV use).

- This group includes new adults, adolescents and all HIV-positive pregnant women (to be initiated on triple therapy, as an FDC, regardless of CD4 count - as per the new PMTCT guidelines anticipated in April 2013)
- Women presenting in the first trimester who require urgent ART initiation for their own health should be managed according to NDoH guidelines. They may not be eligible for the FDC treatment.
- **Note:** Patients weighing <40 kg are unsuitable for the FDC treatment. These patients require **400 mg** EFV (unless concurrently receiving TB treatment). However, should they gain weight, they can be switched to the FDC.

Priority group 2: All HIV-positive pregnant women

- HIV-positive pregnant women who are already stable on 3TC, EFV and TDF should be switched to the FDC treatment
- Breastfeeding women who are stable on individual TDF, 3TC and EFV should be changed to the FDC if they agree to do so.

Priority group 3: Established patients receiving d4T, 3TC and EFV

- All patients who are currently established on individual 3TC, d4T and EFV should be switched to the FDC treatment. Initially, while FDC stocks are built up, patients who display d4T toxicity (most commonly peripheral neuropathy or lipoatrophy) should be prioritised.
- The switch to the FDC treatment should be performed as per existing guidelines. Prior to the switch, clinicians must ensure that the patient has a recent (within 3 - 6 months) **undetectable viral load** and normal creatinine clearance.
- The clinician is effectively switching a single drug, d4T, to TDF; therefore, it is essential to ensure that the patient is virologically suppressed before switching.
- For patients with anaemia precluding AZT use, plus renal dysfunction precluding TDF use, special arrangements must be made to ensure access to d4T or abacavir (ABC).
- Patients should be counselled appropriately about the switch.

- Clinicians must remember to monitor creatinine clearance after 3 and 6 months, respectively, and annually thereafter.

Priority groups 4 and 5: Stable patients with TB co-infection and other co-morbidities

- There is concern that patients with co-morbidities (TB, hypertension or diabetes) may struggle with the combined pill burden.
- To lessen the potential for poor adherence, such patients should be offered the FDC treatment if they are already receiving TDF, 3TC and EFV.
- **Note: Multiple drug-resistant TB (MDR-TB)** patients are **excluded** as aminoglycosides and TDF have overlapping renal toxicity. Rather, these patients should be initiated on AZT or, if anaemic, d4T.
- **Important:** Clinic staff must carefully monitor FDC prescriptions and ensure that sufficient stock is available to secure a continuous FDC supply to all patients being initiated/switched. It is critical that patients do not find themselves being switched back and forth to individual drugs due to insufficient FDC stock.

What about other patient groups?

As SA's ARV programme continues to expand, clinics are experiencing burgeoning populations of stable patients who are clinically well and virologically suppressed. Long-term retention in care of this group is proving problematic and, increasingly, a shift to community-based, adherence club models is being advocated to streamline clinic services and improve patient retention. It is anticipated that successful implementation of such club models would be greatly facilitated by FDC availability, as this would simplify dispensing to club members. However, the NDoH has decided that clinically stable patients receiving TDF, 3TC and EFV are to be prioritised below other groups during the period of this current tender. After allocating FDC stocks to new patients, pregnant patients, d4T-receiving patients and those with co-morbidities, there may not be additional FDC available for stable patients falling into priority groups 6 and 7.

FDC side-effects

Patients taking the FTC/TDF/EFV FDC tablet are expected to experience the same side-effect profile as patients taking the 3 individual drugs. Patients should be counselled about potential side-effects as per usual. Anecdotally, upon switching from individual drugs to other FDCs, some patients report experiencing new or different side-effects. It is uncertain whether this may be associated with the binding components within the co-formulation or due to the psychological effect of changing medication. Most patients will settle with reassurance.

FDC-recipient patients who develop severe adverse events necessitating discontinuation of one agent (e.g. severe EFV-associated central nervous system (CNS) toxicity or TDF-induced renal dysfunction) should be managed as per patients taking individual drugs. Clinicians should adhere to existing guidelines when managing ARV-induced adverse events. If indicated, the FDC treatment should be discontinued to remove the offending agent. The FDC should be replaced with 3 individual drugs: the 2 tolerated drugs plus an alternative to replace the offending drug. The patient must be educated carefully about their new, more complex regimen, including matters such as dosing, expected side-effects and any additional monitoring required.

Note: For FDC-recipient patients who develop **MDR-TB**, clinicians should consider switching the TDF-containing FDC for the duration of aminoglycoside use. If the patient is retained on the FDC treatment, increased renal monitoring should be instituted during the MDR-TB treatment period.

Patient counselling

For patients, the switch from 3 tablets to 1 tablet may raise concerns about efficacy or quality. It is essential that healthcare workers educate patients about the FDC treatment.

Patient counselling messages

- The dosage is one pill once daily, not 3 pills once daily.
- Although the FDC is 'one pill once a day', it does contain 3 different ARV medications – it is easy to take, highly effective and in no way inferior to taking 3 individual drugs.

- Most patients initiating the FDC will not encounter problems, but if they experience any significant side-effects, they should consult their healthcare provider.
- Although the FDC is a large tablet, it is not significantly larger than EFV or LOP/r (Aluvia); therefore, swallowing should not create problems. There is no liquid FDC formulation currently on the market. **Crushing or dissolving the FDC**, which undermines bio-equivalence, **should be avoided**.^[10]
- Patients (especially stable patients) who are not included in the priority groups for the FDC should be counselled so that they understand why they are not being switched to an easier option.

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