



Tenofovir update

October 2008

Department of Health, Western Cape

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health

Department:
Health
REPUBLIC OF SOUTH AFRICA

TDF

NtRTI



once
daily



MCC April 2007
South Africa

Introduction

- tenofovir (TDF) is a nucleotide reverse transcriptase inhibitor – N_tRTI
- used as a substitute for thymidine analogues d4T or AZT (N_sRTIs)
- use restricted due to cost constraints (currently, it is approximately 9 x times more compared to d4T in South Africa) October 2008
- use requires special motivation forms Western Cape



MOTIVATION FOR TENOFOVIR USE



Date of Submission / /

1.

Facility : _____

Prescribing clinician: _____

Contact number: _____

Email address: _____

Signature: _____

2.

Patient Details

Folder number: _____

Surname: _____

First name: _____

Date of birth: / /

Gender: M F

3.

ARV Start Date: / /

Current regimen: [] [] []

Symptomatic Hyperlactataemia

lactate result	date taken
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Severe adverse events on both Zidovudine and Stavudine

Hepatitis B Antigen positive

When test was done	/ /
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Cosmetically significant lipoatrophy

N.B. This motivation **does not** replace an Adverse Event Form, if not yet submitted please complete and fax to 021 483 9921

Planned regimen: [] [] []

Notes:

Send to: HIV/AIDS Pharmacist
Fax: 021 483 9921
Email: Hmoeng@pgwc.gov.za

Date of Review / /

Western Cape
TDF
motivation
form





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Indications



1. patients who require ART and are *HBSAg+*
2. cosmetically significant *lipoatrophy* due to NRTIs
3. symptomatic *peripheral neuropathy* and **CANNOT** use AZT due to pre-existing *anaemia* (Hb < 10) or neutropaenia (<1) **OR** develop anaemia (Hb < 8) or neutropaenia (<1) *after* switching to AZT

HBSAg + = hepatitis B surface antigen positive

Indications



4. symptomatic *hyperlactatemia* or *lactic acidosis* on d4T, AZT or ddi

Note: If severe lactic acidosis ($\text{HCO}_3^- < 15$ mmol/l), patient should rather be restarted on *Aluvia*® and NNRTI ie avoid ALL NRTIs and tenofovir



Dose

12 hourly NVP or *Kaletra*
or *Aluvia*

Tenofovir 300 mg once daily plus
3TC 150mg 12 hourly

OR

TDF 300 mg once daily plus 3TC
300mg once daily

Note: ONCE daily 3TC 42% more expensive

with EFV



3TC = lamivudine

Toxicity and monitoring

- well tolerated with few side effects
- most important described side effect is *nephrotoxicity*
- direct toxicity on renal tubules can cause acute renal failure
- especially in patients with underlying renal dysfunction and those on nephrotoxic drugs (aminoglycosides, amphotericin B, ACE inhibitors and NSAIDs)





Toxicity and monitoring

1. Serum creatinine should be checked and *creatinine clearance* calculated in all patients before starting using *Cockcroft-Gault* equation:

$$\frac{(140 - \text{age}) \times \text{weight}}{\text{Creatinine} \times 0.82}$$

Multiply by 0.85
for women

- if Cr Cl is less than $< 50\text{ml/min}$, AVOID tenofovir
- merely checking serum Cr is NOT sufficient



Toxicity and monitoring

2. Patients started on TDF creatinine clearance should be monitored at 1,2,3 and 6 months, and then 6 monthly ad infinitum
3. Other nephrotoxic drugs should be avoided especially Regime II or MDR TB treatment where an aminoglycoside should not be co-prescribed (all such cases should be discussed with an experienced treater)



Toxicity and monitoring

4. Other – a less common form of renal toxicity is *Fanconi's syndrome*, where patients waste substances from the renal tubule
 - a patient may develop:
 - normoglycaemic glycosuria
 - amino-aciduria
 - hypophosphataemia
 - hypokalaemia
 - *isolated* hypophosphataemia and hypokalaemia have also been described



Toxicity and monitoring

5. muscle symptoms

- weakness
- cramps
- myalgia

} check serum potassium and phosphate

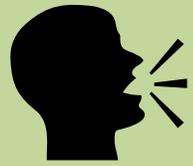
- routine potassium and phosphate is not advised

6. reduction in bone mineral density (no increase in risk fracture but no long term follow up available ?)



Toxicity and monitoring

7. tenofovir and didanosine should not be co-prescribed
 - this combination potentiates ddl toxicity and has been associated with poorer virological and immunological outcomes compared to other NRTI backbones



Toxicity and monitoring

8. *Chronic Hepatitis B* – patients on TDF should not be stopped as this may lead to life-threatening flares of hepatitis B as a result of resurgence of viral replication in the liver

FDA warning

FDA-assigned pregnancy categories

- A = no associated abnormalities in well controlled studies
- **B** = animal studies have revealed no harmful evidence; no risk to human foetus
- C = animal studies show adverse effects
- D = risk shown to human foetus in well controlled studies though benefits may outweigh disadvantages
- E = use *contraindicated* in women of child-bearing age or who are pregnant

FDA = Food and Drug Administration of America

Pregnancy



- TDF classified as a category “B drug”
- are concerns about effects on foetal bone formation in later pregnancy
- not a problem for women who fall pregnant on TDF
- if pregnancy diagnosed, switch to AZT during pregnancy (seldom possible given indications outlined in above programme)

Pregnancy

- pregnant women with previous symptomatic hyperlactataemia or HBSAg+ should NOT switch from TDF to AZT
- they should remain on TDF because of serious risk of re-occurrence of hyperlactatemia or flare of HBV



Children

- TDF is not registered for use in children
- should only be used in Paediatric patients in exceptional circumstances
- its initial prescription is limited to Paediatric HIV specialists

2nd Line – in patients who have used TDF in 1st Line

1. In patients on TDF because of HBV co-infection

- 2nd line = TDF + 3TC + AZT + *Kaletra*
- both TDF and 3TC have antiviral activity against HBV
- 90% of patients on 3TC *monotherapy* for HBV develop resistance within 4 years
- HIV co-infected patients require *dual therapy* TDF and 3TC to prevent development of resistance
- this allows sustained suppression of HBV
- first line of TDF + 3TC + NNRTI (EFV) allows for this

2nd Line – in patients who have used TDF in 1st Line

- when patients on this 1st line develop HIV virological failure, note that standard 2nd line AZT+ddl+Kaletra has NO anti-hepatitis activity
- TDF should not be stopped (can cause liver HBV flare)
- AZT added to boost its anti-HIV efficacy as TDF and 3TC resistance to HIV may have

↑
emerged ↑
K65R mutation M184V mutation

Neither of these 2 mutations compromise AZT (infact, the HIV may be hyper-sensitised to AZT by K65R mutation)

2nd Line – in patients who have used TDF in 1st Line

- therefore **four** ART drugs are used:
- continued dual therapy of HBV with TDF + 3TC
- suppressive HIV activity with robust *Kaletra* and fully active AZT
- TDF + 3TC may continue to add *partial* anti-HIV activity to the regime

2nd Line – in patients who have used TDF in 1st Line

- 2. Patients who have switched to TDF because of hyperlactataemia, lactic acidosis or severe lipoatrophy
- 2nd line = **TDF + 3TC + Kaletra**
- if previous hyperlactataemia or lactic acidosis, risk of reoccurrence of this toxicity with AZT, d4T or ddI
- avoid these *three* drugs in 2nd line
- TDF and 3TC may be compromised with *mutations*
- there will be *residual activity* from TDF even with K65R

2nd Line – in patients who have used TDF in 1st Line

- TDF has a partially suppressive effect with K65R, and this is potentiated when M184V is also present and 3TC is maintained in the regime
- avoid AZT as it might cause hyperlactataemia or lactic acidosis to recur
- avoid AZT as it may cause lipoatrophy to worsen
- *toxicity concerns here take precedence over option of adding AZT for its anti-HIV effect*

2nd Line – in patients who have used TDF in 1st Line

- 3. Patients who have switched to TDF for neuropathy on d4T and anaemia or neutropaenia on AZT
- 2nd line = **TDF + 3TC + Kaletra**
- AZT likely cause anaemia or neutropaenia to recur
- ddi could cause neuropathy to worsen or recur

Summary



- all these cases (1), (2) and (3) should be discussed with an expert as flexibility could be applied in individual cases
- eg a patient who had only *mild* hyperlactataemia *without* acidosis due to d4T in 1st line, AZT could be considered in 2nd line together with TDF, 3TC and *Kaletra* with *close monitoring*
- ongoing analysis of motivations received may result in revision of these guidelines

WC - 350 cases in
first 2 months : Oct' 08



Prices of ART – October 2008

Reg		d4T 30mg bd	3TC 150 mg bd	3TC 300 mg daily	EFV	NVP	AZT	TDF	ddl	<i>Kaletra Aluvia</i>	TOTAL Price (R)
	P R I C E	17.65	29.91	42.50	108.03	32.11	71.09	159.49	67.83	319.07	
1a		1	1		1						155.59
1b		1	1			1					79.67
1a TDF				1	1			1			310.02
1a AZT			1		1		1				209.03
2							1		1	1	457.99

TDF = tenofovir

1a (EFV) per year = R1867.08

1b per year = R 956.04