RATIONALE FOR TENOFOVIR AS THE FIRST CHOICE IN THE FIRST-LINE TREATMENT OF HIV

BACKGROUND

In its 2006 revision of the Guidelines on Antiretroviral Therapy for HIV Infection in Adults and Adolescents, the World Health Organization (WHO) recommended that countries begin planning to move away from stavudine (d4T)-containing regimens to avoid or minimize the risk of toxicity.[i] In the 2010 revision, WHO reinforced the need for countries to phase out stavudine-based regimens because of the drug's long-term irreversible side effects. In its place, WHO suggests using zidovudine (AZT) or tenofovir (TDF)-based first-line regimens.[ii]

Of these two options, TDF, a nucleoside reverse transcriptase inhibitor, has a number of advantages: it is well tolerated and requires minimal laboratory monitoring.[iii] Further, the price of TDF has recently come down substantially.

Several African countries adopted TDF as first-line therapy as early as 2007. According to WHO, almost all (97%) low- and middle-income countries are in compliance with the WHO recommendation to shift away from stavudine-containing regimens,[iv] and around half have opted for a TDF-based first-line treatment of HIV.[v]

This document summarizes the advantages of using a TDF-based regimen when switching from stavudine (d4t), as well as when initiating adult antiretroviral therapy (ART).

CLINICAL ADVANTAGES OF TENOFOVIR

1. **Tolerability:** TDF is well tolerated. The main advantage over AZT is that it does not cause anaemia[vi] and this has led—in Médecins Sans Frontières' (MSF) experience—to better tolerability. For example, in a routine treatment cohort in Lesotho, patients on AZT were more than twice as likely to experience a toxicity-driven regimen substitution compared to TDF.[vii] The main concern with TDF use is renal toxicity, although it is not clear to what extent renal screening and monitoring is required. Data from a recent systematic review of TDF use (17 studies, including 9 randomized trials) concluded that, while TDF was associated with a statistically significant loss of renal function, the clinical magnitude of this effect was modest, and thus regular monitoring of renal function was not considered a precondition for TDF use.[viii] This is supported by data from an MSF-supported program in Lesotho, which found that TDF-associated renal toxicity was rare and mainly transient.[ix] The other concern with TDF use is bone mineral loss, but there is no high-quality evidence to suggest that patients who are at higher risk of fracture should not receive tenofovir. [x]

2. **Adherence:** TDF is available as a once-daily fixed-dose combination (FDC), both of which have been associated with better patient adherence compared to multiple pills[xi] or twice daily regimens.[xii] [xiii]

3. **Hepatitis B:** TDF is also active against hepatitis B, which makes it the treatment of choice for HIV/hepatitis B co-infected patients.[xiv,xv]

4. **Resistance**: TDF appears to be more robust towards acquisition of resistance-associated mutations.[xvi]

5. **Pregnancy:** TDF can be used during pregnancy, as it is classified by the US Food and Drug Administration (US FDA) as pregnancy class B, indicating that there is no evidence in animal studies of fetal risk.[xvii] According to the Antiretroviral Pregnancy Registry, in utero exposure to TDF is not associated with increased prevalence of congenital abnormalities.[xviii] The triple fixed-dose combination that includes TDF, which involves taking just one pill once a day, is paired with efavirenz (EFV), for which there are some concerns about safety during the first trimester of pregnancy. The WHO 2010 guidelines allow prescribing of EFV during second and third trimester of pregnancy, but recommend avoiding the use of EFV during the first trimester of pregnancy unless effective contraception is provided, because of concerns about a potential increased risk of birth defects.[xix] However, this risk is based on low-quality evidence and not supported by systematic reviews. A recent meta-analysis found no increased risk of overall birth defects among women exposed to EFV during the first trimester of pregnancy compared to exposure to other antiretroviral agents. Prevalence of overall birth defects with first trimester EFV exposure: 2.0%, 95% CI 0.8–3.2. The prevalence of neural tube defects was also low (0.07%, 95%CI 0.002-0.39%); however the limited sample size for detection of rare outcomes such as neural tube defects prevents a definitive conclusion.[xx] Ultimately, the use of EFV in pregnancy requires a decision based on the balance of clinical and programmatic risks and benefits. The British HIV Association (BHIVA) new draft guidelines, issued in February 2012, reverse an earlier recommendation against use of efavirenz in the first trimester: "[b]ased on the emerging prospective data in which no evidence of human teratogenicity has been seen, the panel consider that there are insufficient data to support the former position and furthermore recommend that efavirenz can be both continued and commenced in pregnancy."[xxi]

6. **TDF and children**: In January 2012, the US FDA approved the use of tenofovir in children older than 2 years of age.[xxii] This will allow for harmonization of treatment for adults and children over a certain age through the use of scored FDCs.[xxiii] Guidance on scoring of existing FDCs and specification of other FDCs for certain weight and age groups of children is now needed from WHO.

PRICE AND PRACTICAL ADVANTAGES OF TENOFOVIR

Tenofovir is cost effective and easier to take → Available As One-Pill-Once-A-Day Combination

Pricing of antiretrovirals (ARVs) has been a major factor in determining the choice of regimens in HIV programs in developing countries. The latest edition of MSF's ARV pricing report, *Untangling the Web of Antiretroviral Price Reductions 14th edition*, shows several ARVs have undergone significant price reductions over the last few years (see Annex 1).[xxiv]

The price of TDF has come down significantly over the last three years—more so than the price of AZT—and TDF and TDF-based regimens are now cheaper than AZT and AZT-based regimens. Compared to 2008, the price of single-drug TDF had decreased by 52% by 2011, and the price of the triple FDC of TDF/3TC/EFV had decreased by 53% to US$173 ppy. The price of the double FDC TDF/3TC co-packed with EFV is $143 ppy. The price decrease of tenofovir-based combinations over the past three years could be the result of an increase in demand and volume for TDF for first- as well as second-line treatment. Data sourced from the Global Fund to Fight AIDS, TB, and Malaria's Price and Quality Reporting database showed an increased amount of TDF triple FDCs procured with Global Fund funds in 2011 in a number of countries.[xxv]

In addition to price reductions, the superior side-effect profile of TDF compared to AZT translates into programme costs savings. Data from MSF's programme in Lesotho show that people on TDF were six times less likely to experience side-effects compared to patients on d4T, and the risk of side-effects on TDF was halved compared to patients on AZT.[xxvi] A modelling study in India found that given the costs of managing side effects of d4T, TDF is cost-effective.[xxvii] Further, MSF's cost effective analysis found that TDF-based regimens were linked with higher life years and quality-adjusted life years (QALYs).[xxviii]

The regimen TDF/3TC/EFV has additional advantages over alternatives: once-a-day dosing can help support adherence; the regimen is not contraindicated for patients on TB treatment, unlike those containing the NNRTI nevirapine (NVP); and the pricing is competitive with AZT-containing regimens that include EFV.

TDF – PRICES AND PILL BURDEN AT A GLANCE:

Regimen	**Combination**	**Pills per day**	**Dosing**	**Price ppy**
TDF with EFV	TDF/3TC/EFV	One	1 pill/once a day	$ 173
TDF with EFV	TDF/3TC plus EFV	Two	2 pills/once a day	$ 143
AZT with EFV	AZT/3TC plus EFV	Three	1 pill/twice a day+ 1 pill/once a day	$ 153
TDF with NVP	TDF/3TC plus NVP	Three	1 pill/once a day +1 pill/twice a day	$ 122
AZT with NVP	AZT/3TC/NVP	Two	1 pill/ twice a day	$ 132

The table below provides a detailed overview of prices and formulations of TDF and AZT-based regimens.

Annex: Prices reported in *Untangling the Web of Antiretroval Price Reductions*, 14th Edition, July 2011

TDF	Daily	Gilead		Aspen	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides				
		Cat 1	Cat 2											
300mg tab	1	**204(0.559)**	**360(0.986)**	87(0. 237)	**88(0.242)**	**83(0.227)**	**103(0.283)**	**76(0.208)**	**97(0.267)**	79(0.217)				
AZT	Daily	ViiV	Aspen	Aurobindo	Cipla	Hetero	Matrix	Micro Labs	Ranbaxy					
300mg tab	2	**301(0.412)**	**99(0.136)**	**88(0.121)**	**91(0.125)**	**100(0.137)**	**88(0.121)**	**91(0.125)**	**91(0.125)**					
NVP	Daily	BI		Aspen	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides				
		Cat 1	Cat 2											
200mg tab	2	**219(0.300)**	**438(0.600)**	**37(0.051)**	**37(0.050)**	**39(0.054)**	**37(0.050)**	**31(0.043)**	**37(0.050)**	**32(0.044)**				
EFV	Daily	Merck		Aspen	Aurobindo	Cipla	Emcure	Hetero	Matrix	Micro Labs	Ranbaxy	Strides		
		Cat 1	Cat 2											
600mg tablet	1	**237(0.650)**	**None**	62(0.170)	**73(0.200)**	**79(0.217)**	**61(0.167)**	**67(0.183)**	**55(0.150)**	58(0.158)	**72(0.197)**	**52(0.143)**		
3TC/d4T	Daily	Cipla	Hetero	Matrix	Ranbaxy	Strides								
150mg/30mg tab	2	**42(0.058)**	**46(0.063)**	**39(0.054)**	**42(0.058)**	**41(0.056)**								
AZT/3TC	Daily	ViiV	Aurobindo	Cipla	Hetero	Matrix	Micro Labs	Ranbaxy	Strides	Varichem				
300mg/150mg tab	2	**231(0.316)**	**107(0.147)**	**104(0.142)**	**110(0.150)**	**101(0.138)**	**112(0.154)**	**110(0.150)**	**123(0.169)**	**107(0.147)**				
TDF/FTC	Daily	Gilead		Aurobindo	Cipla	Hetero	Matrix							
		Cat 1	Cat 2											
300mg/200mg tab	1	**315(0.863)**	**540(1.479)**	**140(0.383)**	134(0.367)	164(0.450)	**116(0.317)**							
TDF/3TC	Daily	Aurobindo	Cipla	Hetero	Matrix									
300mg/300mg tab	1	**116(0.317)**	**103(0.283)**	**116(0.317)**	**91(0.250)**									
3TC/d4T/NVP	Daily	Cipla	Hetero	Ranbaxy	Strides	Varichem								
150mg/30mg/200mg tab	2	**64(0.088)**	**67(0.092)**	**70(0.096)**	**66(0.090)**	**61(0.083)**								
AZT/3TC/NVP	Daily	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides							
300mg/150mg/200mg tab	2	**144(0.197)**	**137(0.188)**	**143(0.196)**	**134(0.183)**	**140(0.192)**	**141(0.193)**							
TDF/3TC+NVP	Daily	Matrix												
300mg/300mg + 200mg (co-pack)	1kit (3 tablets)	**134(0.367)**												
TDF/FTC/EFV	Daily	BMS/Gilead/ Merck		Cipla	Hetero	Matrix								
		Cat 1	Cat 2											
300mg/200mg/600mg tab	1	**613(1.680)**	**1033(2.830)**	231(0.633)	243(0.667)	**219(0.600)**								
TDF/3TC/EFV	Daily	Cipla	Matrix											
300mg/300mg/600mg tab	1	195(0.533)	**173(0.475)**											

Note:

- Quality is an important factor and price should not be the only factor determining procurement decisions. The products in the table with prices in bold were either WHO Prequalified or US FDA tentatively approved as of June 2011. For more information please refer to http://apps.who.int/prequal/ and http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm
- All prices are quoted in USD. In brackets is price per unit e.g. tablet or capsule and figure not in brackets are price per patient per year calculated based on dose required per day x 365 days per year.

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