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The use of Tenofovir Disoproxil Fumarate (TDF) in HAART regimens

Clinical uses of tenofovir

Tenofovir (TDF) has just become available in South Africa. It is a nucleotide reverse transcriptase inhibitor. It differs from the nucleoside reverse transcriptase inhibitors (NRTI, e.g. zidovudine) only by having a phosphate group. Like the NRTIs it needs to be further phosphorylated intracellularly in order to be active and then acts by mimicking the building blocks of DNA. It has similar moderate potency to the other NRTIs. In many respects it is similar to stavudine and zidovudine in that several mutations are often necessary for resistance, and that this resistance can be partially overcome by the addition of lamivudine (3TC) or the very similar NRTI emtricitabine (FTC - see below).TDF is available as a single agent (Viread®) or co-formulated with FTC (Truvada®).

TDF has a long half life, allowing once daily dosing. This convenient dosing, together with a low rate of side effects (see below), have made TDF a popular choice as a component of combination antiretroviral therapy. For practical purposes, TDF should always be used together with either 3TC or FTC. TDF should not be used with didanosine due to an adverse drug interaction (see below) and high virological failure rates.

In first line therapy AfA recommends either zidovudine (AZT) plus 3TC, or TDF plus FTC (or 3TC) as the dual NRTI combination together with a non-nucleoside reverse transcriptase inhibitor. Stavudine plus lamivudine is associated with an increased risk of toxicity (peripheral neuropathy, lipo-atrophy and hyperlactataemia) and is best avoided if possible, although this is the cheapest dual NRTI combination. TDF in combination with either FTC or 3TC generally retains significant efficacy in second line regimens with boosted protease inhibitors. Rational use of TDF in salvage therapy generally requires the use of resistance testing. AfA authorizes antiretroviral resistance tests in selected patients (it is essential for reimbursement purposes that this expensive test is authorized). A review of these tests shows that tenofovir (with either 3TC or FTC) is very often the best dual NRTI combination in second line or salvage therapy. This is not surprising as it has not been widely available. Our experience in the next few years will be interesting.

Resistance patterns associated with decreased tenofovir efficacy

1. There are 3 key resistance patterns affecting TDF: The K65R mutation is associated with resistance to TDF, abacavir, didanosine, and 3TC/FTC. K65R reduces TDF susceptibility approximately 2 –fold. Co-administration with 3TC / FTC partially restores TDF sensitivity.

2. Mutations associated with resistance to stavudine and zidovudine, otherwise known as Thymidine Analogue Mutations (TAMs), may compromise the use of TDF. It is the combination of TAMs that it is important, specifically the combination of the M41L, L210W and T215Y mutations. This combination (and in particular the first two mutations) decrease TDF efficacy by approximately 4 fold. As with the K65R mutation, co-administration with 3TC / FTC partially restores TDF sensitivity when these TAMs are present. Other TAMs (D67N, K70R, K219Q/E) do not compromise TDF activity.

3. The multi-NRTI insertion complex T69S causes high level resistance to all NRTIs including TDF. Co-administration of FTC/3TC does not improve susceptibility with this insertion complex.

Emtricitabine (FTC)

FTC is co-formulated with tenofovir in Truvada®. FTC is very similar to 3TC. Like 3TC, it is also active against hepatitis B. The same resistance mutations impair FTC and 3TC for both HIV and hepatitis B. FTC has a longer intracellular half life than 3TC (39 versus 20 hours), but both agents can be given once daily. As with 3TC, it is generally well tolerated, however hyperpigmentation, usually involving the palms and soles, occurs with FTC.

Tenofovir: Side effects and toxicities

Tenofovir (TDF) is a drug that is generally well tolerated initially, causing minimal gastro-intestinal disturbance in a minority of patients. Concerns regarding TDF relate to the risk of it causing nephrotoxicity, reductions in bone mineral density and its use in pregnancy.

There are several case reports of TDF causing acute renal failure and Fanconi's syndrome owing to its toxic effects on renal tubules. There have also been reports of TDF causing hypokalaemia. Fanconi's syndrome results from renal tubular wasting of substances and may manifest with proteinuria, hypophosphataemia, hypouricaemia and/or normoglycaemic glycosuria. It may or may not be associated with a rise in serum creatinine and manifests with non-specific symptoms such as lethargy. TDF nephrotoxicity has occurred almost exclusively in patients with abnormal renal function when they start the drug and/or those simultaneously on other nephrotoxic drugs such as amphotericin-B. These toxicities are reversible in most patients upon stopping the drug. AfA thus advises that the serum creatinine is measured and the creatinine clearance calculated in all patients before starting TDF.

Cockgraft-Gault equation to estimate creatine clearance (the eGFR can also be used):

$$\frac{(140 - \text{age}) \times \text{ideal weight (kg)}}{0.82 \times \text{serum creatinine } (\mu\text{mol/L})}$$

Good estimate for men, for women multiply total by 0.85.

In those with a calculated creatinine clearance (or eGFR) < 50ml/min TDF should be avoided. In addition, the serum creatinine should be rechecked at 3 months and 6 months and then 6 monthly in patients started on the drug. It is also prudent to check urine dipstix at these time points.

TDF has been associated with reductions in bone mineral density, but this has not equated into an increased fracture risk in studies. However, the follow-up time may have been too short to ascertain this. This has led to concerns regarding the use of TDF in children for which it is not registered. Although TDF is classified by the FDA as a Category B drug in pregnancy, there are concerns regarding its effects on foetal skeletal development and there is limited experience with its use in pregnancy.

TDF is a nucleotide reverse transcriptase inhibitor (NtRTI) and thus has the theoretical potential to cause mitochondrial toxicity like the nucleoside reverse transcriptase inhibitors (NRTIs). However, in vitro studies show that its propensity for mitochondrial toxicity is far less than that of stavudine, didanosine and zidovudine. In clinical settings TDF has not been implicated in causing lactic acidosis unless there are co-factors such as renal failure or other higher risk NRTIs being used concomitantly. It does not cause pancreatitis nor neuropathy. The rates of lipoatrophy on TDF are far lower than for stavudine (3 vs 19% respectively at 3 years in the Gilead 903 study). TDF is thus an option to use in patients who have developed mitochondrial toxicities on NRTIs. However, TDF should be avoided after life-threatening lactic acidosis. Patients who have experienced symptomatic hyperlactatataemia from other NRTIs that was not life-threatening may be challenged with TDF plus either FTC or 3TC provided their lactate has returned to normal and with regular monitoring of lactate for several months.

Hepatitis B

Tenofovir has activity against hepatitis B, as does 3TC and FTC. Although it is not currently registered for treating hepatitis B, initial studies show significant activity. International guidelines recommend using tenofovir together with either 3TC or FTC in patients co-infected with hepatitis B and HIV, and who need antiretroviral therapy[1]. It is likely that therapy with tenofovir plus 3TC/FTC will delay the emergence of hepatitis B resistance. Large phase 3 trials are currently underway, with results expected this year.

Of great importance is that stopping tenofovir (or FTC/3TC) can trigger severe flares of hepatitis B, which may be life-threatening. This is a "black box" warning in the package insert[2]. Hepatitis B co-infected patients who fail their antiretroviral tenofovir-containing regimen must continue tenofovir (and FTC/3TC) for the hepatitis B. Thus it is important to establish the hepatitis B status (surface antigen is a useful screening test) of all patients going on to tenofovir.

References

1. Soriano V et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV–HBV International Panel. AIDS 2005, 19:221–240

2. Thio CL et al. Treatment of Chronic Hepatitis B in HIV-Infected Persons: Thinking Outside the Black Box. Clin Infect Dis 2005; 41:1035–40

The use of tenofovir in pregnancy and in paediatric patients

NB: *There are concerns about TDF's effect on bone mineral density, which appears to be more severe in children.*

Pregnancy

Tenofovir is classified in Category B for risk of teratogenicity (animal studies have failed to demonstrate a risk to the foetus but there are no adequate well-controlled studies). Doses up to 14 times that given to humans have shown no teratogenicity in rats and rabbits. Long-term administration to 4 gravid rhesus macaques at 30mg per kg per day showed alterations both in maternal biomarkers and reduced foetal bone porosity.[1] Until there are more data, tenofovir is best avoided in pregnant women. The safest NRTIs to use in pregnancy remain zidovudine and lamivudine.

Children

There are limited data for children and tenofovir is not recommended for those <18 years of age. Dosages in clinical trials for children aged 2 to 8 years have used 8mg/kg/day and for those between 8 and 18 years, 210mg/m^2 (max 300mg). Nevertheless, tenofovir has been used in children, especially for lipoatrophy where stavudine is replaced[2] and as part of salvage therapy.[3] For the latter, >6% loss of bone mineral density occurred in 5 of 15 subjects after 12 months of use.[3]

References

1. Tarantal AF, Castillo A, Ekert JE, Bischofberger N, Martin RB. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). J Acquir Immune Defic Syndr 2002;29(3):207-20.

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Monitoring patients on tenofovir

AfA recommends the following tests:

Prior to initiating TDF:

1. Serum creatinine and eGFR
2. Hepatitis B surface antigen

Patient on TDF:

1. Serum creatinine 3 months after starting TDF and then 6 monthly

Viread® and Truvada®

Viread® and Truvada® have recently been registered in South Africa.

Viread® tablets contain 300mg of tenofovir per tablet. The dose is one tablet once daily. The tablet may be taken with / without food, but fatty meals increase absorption by 40%.

Cost: R199.29 (single exit price incl. VAT)

Truvada® tablets are a combination tablet containing 200mg of emtricitabine and 300mg of tenofovir per tablet. The dose is one tablet once daily with or without food.

Cost: R329.89 (single exit price incl. VAT)

Tenofovir drug interactions

Unlike the nucleoside reverse transcriptase inhibitors (NRTI), tenofovir is involved in several potentially important drug interactions. The most important of these occur with other antiretrovirals:

- Didanosine (ddI) concentrations are increased, with increased risk of pancreatitis. The ddI dose must be reduced (from 400mg to 250 mg in patients >60 kg), but this combination has been shown to be inferior to other dual NRTI combinations and is **NOT** recommended.

- Atazanavir concentrations are significantly reduced, resulting in a high risk of subtherapeutic trough concentrations – this can be overcome with ritonavir boosting. Atazanavir **MUST** be given with ritonavir if tenofovir is co-administered.

- Tenofovir concentrations are significantly increased when co-administered with ritonavir-boosted protease inhibitors. The clinical significance of this interaction is uncertain. Renal function should be closely monitored.

Interactions with other drugs:

- Avoid use of other nephrotoxic drugs (e.g. amphotericin B, aminoglycosides) if possible.

- Concentrations of acyclovir, valaciclovir, valganciclovir and ganciclovir may be increased – monitor for toxicity.

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