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In this issue:

Tenofovir and *Truvada* – what to do with them if you can get your hands on them?; *page 2*

- Tenofovir and Truvada approved in South Africa
- Quick and dirty clinical review
- Chemistry and pharmacokinetics
- Anti-HIV activity
- Tenofovir as part of a triple nucs combination?
- Anti-hepatitis B activity
- Switching to tenofovir or *Truvada* to improve ART-tolerance
- Tenofovir or Truvada side-effects
- Tenofovir and kidney toxicity
- Bone mineral density
- Tenofovir's safety in children and during pregnancy
- Drug interactions
- Tenofovir resistance – and the implications for sequencing
- So when should tenofovir be used?
- How much will access really improve?
- References

Tenofovir and *Truvada* — what to do with them if you can get your hands on them?

Tenofovir and *Truvada* approved in South Africa

On Friday, April 13 2007, the South African Medicines Control Council (MCC) granted regulatory approval to three new once-a-day generic formulations from Aspen Pharmacare, *Viread* (tenofovir disoproxil fumarate), *Emtriva* (emtricitabine — a cytosine nucleoside analogue considered more or less interchangeable with 3TC (lamivudine))— and *Truvada*, a fixed-dose coformulation of tenofovir and emtricitabine.

Although these aren't the only new antiretrovirals to be approved by the MCC of late — for instance, a handful of new generic formulations of lamivudine and zidovudine (AZT), and even GSK's newish protease inhibitor, *Telzir* (fosamprenavir) have been approved over the last several months — the tenofovir-related approvals are perhaps the most highly anticipated because of the need for a more easily tolerated alternative to zidovudine and d4T (stavudine). In fact, revised WHO guidelines now recommend tenofovir as part of the first-line nucleos(t)ide analogue component of antiretroviral therapy (ART) wherever it is available and affordable because of its "excellent safety profile and ease of use" (see <http://www.who.int/hiv/pub/guidelines/adult/en/index.html>).

Quick and dirty clinical review

With the promise (at least) of improved access, a short review of the published data on these drugs may be in order. This will focus primarily on the tenofovir disoproxil fumarate component of *Truvada*, simply because most sources suggest that emtricitabine's resistance, activity and toxicity profile is very similar to lamivudine (though it may have a somewhat longer intracellular half-life).

Chemistry and pharmacokinetics

Tenofovir disoproxil fumarate is the prodrug of tenofovir. Much used to be made of the fact that tenofovir, as a nucleotide analogue belongs in a separate class of antiretroviral than nucleoside analogues. Essentially, this means the drug undergoes one less step to be converted into its active metabolite. But this doesn't appear to make any real functional difference — for instance, data suggest that some nucleoside analogues, in particular emtricitabine, lamivudine and abacavir, were more potent inhibitors of reverse transcriptase in phase I dose-ranging studies. However, tenofovir does have an unusually long half life - 17 hours in serum and 60 hours within the cell - allowing it to be taken once-a-day (at a dose of 300mg) (Kearney 2004). One report that the half-life is even longer (around 7.5 days) suggests that, in order to prevent resistance, that caution should be exercised if the drug should ever have to be discontinued. Meanwhile, emtricitabine's plasma half-life ranges from six to nine hours, but its active metabolite has a half-life of 39 hours permitting once daily dosing as well (Wang) (at a dose of 200mg per day) — and for the two drugs to be given (and coformulated) in a once-a-day regimen.

Anti-HIV activity

Tenofovir-containing regimens have been shown to have comparable activity to similar first-line regimens containing AZT (Gazzard) (and see

<http://www.aidsmap.com/en/news/A7112741-3E70-4AF7-9469-C77C1C644FBA.asp>), and d4T (Gallant 2004) as well as in treatment experienced patients (Gallais 2004, Squires 2003, Schooley 2002). (It should be noted that these studies took place in Western settings where HIV-1B is the predominant clade of virus).

However, two studies have reported disappointing results on at least one tenofovir regimen: tenofovir/3TC and nevirapine, all given once a day (Rey 2007, Towner 2004) — with twice-daily regimens performing better. It is unclear whether poor tolerability of once-daily nevirapine, or lower than adequate trough concentrations of any of the drugs led to the poor performance of this regimen.

Tenofovir as part of a triple nucs combination?

One potential benefit of having tenofovir available, according to WHO at least, is that it may permit the construction of triple nucleos(t)ide reverse transcriptase inhibitor (NRTI) regimen (in addition to abacavir/AZT/3TC) as an alternative for first-line ART in situations where non-nucleoside reverse transcriptase inhibitors (NNRTIs) cause complications, while preserving the PI class for second-line treatment. Results to date for most such regimens have been disappointing compared to NNRTI or PI-based ART (Gallant 2003; Landman 2004, Elion 2004), and combinations with some nucleoside analogues may actually be antagonistic (ddl) or increase the likelihood of resistance developing (abacavir). In fact, the only tenofovir-containing triple NRTI regimen that WHO recommends is tenofovir/AZT/3TC (presumably interchangeable with emtricitabine), which was deemed to perform acceptably in the DART study.

DART is an ongoing large trial in over 3000 people in Uganda and Zimbabwe, that is investigating the use of laboratory markers to monitor patients and involves a few ART regimens. Data on a virological substudy in 300 patients on tenofovir/AZT/3TC suggest that at 48 weeks, 65% of patients had viral loads below 400 copies/ml and 50% had viral loads below 50 copies/ml (Kaleebu see

<http://www.aidsmap.com/en/news/5DE0173C-C055-4FCC-A6B4-C6AC6B5169C4.asp> and

<http://www.aidsmap.com/en/news/2DBF77C1-BED4-4DE1-A94E-E7838592E65F.asp>. A small French study recently demonstrated similar results for the regimen (Rey 2006) — though it is arguable whether the regimen performs anywhere near as well as NNRTI-based ART or is as easy to tolerate as efavirenz/*Truvada* (see <http://www.aidsmap.com/en/news/EA187425-E2E3-48CE-A5C5-8EF8C71B0D5E.asp>).

Nevertheless, WHO suggests that there may be situations where a triple NRTI regimen might be considered: for example, in women with CD4 counts of 250–350 cells; coinfection with viral hepatitis or tuberculosis; severe adverse reactions to NVP or EFV, or in people with HIV-2.

Anti-hepatitis B activity

Despite not being licensed for the indication, both tenofovir and emtricitabine also have potent activity against the hepatitis B virus (HBV). Studies have shown that tenofovir is just as effective against

HBV as adefovir, although HBV can develop resistance to tenofovir (Sheldon 2004; van B  l 2004). Use of tenofovir in HIV / HBV co-infected people showed a significant drop in HBV viral load and, in some cases, clearance of the HBV (Ristig 2002; Nelson 2003). It also appears to reduce levels of HBV DNA in the blood of people with HBV resistant to 3TC (Neff 2004). An analysis of a subset of patients enrolled in Study 903 has shown that combination treatment with tenofovir and 3TC was more effective in treating HBV than 3TC alone (Dore 2004).

FTC monotherapy has shown promising results in HIV-negative people with HBV, with 64% of patients taking the 200mg daily dose achieving undetectable HBV at 36 weeks (Rousseau 2001). It also has shown potent activity against both HBV and HIV in co-infected individuals (Harris 2004).

Because of their activity against HBV, clinicians should be aware of the risk of hepatitis flares should either drug have to be discontinued.

Switching to tenofovir or *Truvada* to improve ART-tolerance

At least some of tenofovir's good performance in most of these studies can be attributed to its superior side-effect profile – with fewer people dropping out or failing to adhere to tenofovir-containing regimens. In addition, the greatly reduced incidence of metabolic effects (such as lipoatrophy) has made tenofovir an appealing option for patients suffering from these complaints (Cheng 2002, Gallant 2004).

Several studies have demonstrated significant improvements in side effects from other nucleoside analogues after switching to tenofovir. In one more recent study, which also reported that patients on efavirenz-based regimens who switched to *Truvada* after at least eight weeks on *Combivir* increased the chances of achieving a viral load below 50 copies/ml (de Jesus), there were also modest but significant improvements in levels of total cholesterol, LDL cholesterol and triglycerides, and patients reported less fatigue and an improvement in the quality of life.

In another study, there were significant reductions in d4T-associated cholesterol and triglyceride levels in patients switched to tenofovir (Moreno 2003). Likewise, another study found that people who switched from d4T to tenofovir after three years of d4T treatment regained a significant amount of limb fat – almost one kilo after two years of tenofovir treatment (Madru  a). Patients in the same study treated with tenofovir for up to five years reported no fat loss (Cassetti).

Tenofovir or *Truvada* side-effects

This does not mean however that tenofovir and emtricitabine are completely without side-effects. In fact, many of the same short-term complications seen with other nucleoside analogues including nausea, vomiting, diarrhoea and flatulence and dizziness can all occur, though perhaps to a lesser extent.

However, healthcare workers and patients may need to keep an eye on two other potential side-effects: kidney side-effects and, possibly bone weakening (decreasing bone mineral density).

Tenofovir and kidney toxicity

Since it was first developed, there have been fears that tenofovir might cause kidney damage because this is a severe side effect of two chemically related drugs, adefovir and cidofovir. In addition, dose-limiting toxicity was seen in preclinical studies with dogs at levels exceeding five times the dose given to humans.

So researchers have closely monitored ongoing studies for any sign of this toxicity. Thus far, what they have found is that kidney malfunction does seem to occur at a slightly higher rate on tenofovir than on other drugs, but it only seems to affect a minority of patients (around 4%), many of whom have histories of mild renal impairment (possibly related to genetic factors) or who are on other nephrotoxic drugs, such as amphotericin B. In addition, the kidney-related side-effects are usually mild and reversible.

However, given the high rate of pre-existing kidney disease among the HIV-infected population in Africa, and the occurrence of a couple of documented deaths due to kidney failure in these studies (see <http://www.aidsmap.com/en/news/EA0A3CB2-FE5A-474A-B09A-7C-FB467965CC.asp>), it will be necessary to perform regular monitoring of blood levels of creatinine (or creatinine clearance rate/glomerular filtration rates (GFR)) and electrolytes (serum phosphate) in patients receiving tenofovir.

Tenofovir should not be used in patients with baseline creatinine levels above 1.5mg/dl (132  M), and patients with reduced creatinine clearance (<50ml/min) should increase the dosing interval to 48 hours or longer.

People taking tenofovir should be advised to conduct their doctor immediately if they begin to experience symptoms of extreme thirst, frequent urination, confusion or muscular weakness.

More complete discussion of tenofovir-related kidney toxicity can be found here (see <http://www.aidsmap.com/cms1174671.asp>). In addition, data from recent conferences can be found here (see <http://www.aidsmap.com/en/news/538244AD-0FCD-4FBA-8250-34F45FBF379F.asp>, <http://www.aidsmap.com/en/news/1689492A-90C4-4A59-A891-8117356FC545.asp>, <http://www.aidsmap.com/en/news/57FE906C-A5F4-4654-A994-0EB397E4C44D.asp> and <http://www.aidsmap.com/en/news/B19ACD5D-29AC-410F-9AB9-3ED699784533.asp>).

Bone mineral density

There are some concerns that a gradual loss of bone mineral density in patients on tenofovir may come to have more significance in the long run.

Findings from animal studies have raised concerns about a possible deleterious effect of tenofovir on bone mineral density – which could be the result of Fanconi syndrome, a disruption of the normal filtering processes that take place in the tubes of the kidneys. This may lead to bone disease due to a lack of resorption in the kidney tubules of substances such as calcium, which are essential for bone maintenance. If this process is cumulative in some patients on tenofovir, it could lead to an increased risk of osteoporosis and fractures – especially as people with HIV age.

In Gilead's Study 903, there was greater bone mineral loss in the spine after three years of treatment, but not in the hip, in tenofovir-treated patients but patients who received d4T for the first two years of the study before switching to tenofovir experienced significantly greater reductions in hip bone mineral density (Madru  a).

There may be ways to manage this complication however. For example, at the recent Conference on Retroviruses and Opportunistic Infections, there was a study suggesting that alendronate, given in combination with vitamin D and calcium could improve bone mineral density in HIV-infected patients (McComsey) (see

<http://www.aidsmap.com/en/news/5B308DE1-D18B-4D7E-B48F-44EA40B6B598.asp>.

Tenofovir's safety in children and during pregnancy

The possibility of bone toxicity might not bode well for tenofovir's use in children or for the prevention of mother-to-child transmission. Initial tenofovir studies in infant monkeys were quite discouraging. Monkeys who were given tenofovir during the early days of life had a high risk of stunted growth and bone toxicity (Tarantal 1999). Likewise, one study of tenofovir in pregnant monkeys found some evidence that infant size, weight and bone porosity were reduced in infants exposed to tenofovir. Circulating levels of insulin-like growth factor were also significantly lower in the exposed infants (Tarantal 2002).

Since that time, studies in children have generated somewhat mixed results. One small study in 16 HIV-positive children aged between six and 18 years of age suggested that tenofovir had no negative effects (Giacomet).

In contrast, a small but rigorous NCI/NIH study presented as a poster at the Conference on Retroviruses and Opportunistic Infections concluded that, despite linear growth, five out of six children treated with tenofovir (as part of a ritonavir-boosted protease inhibitor-based regimen) experienced absolute decreases in bone mineral density with worsening bone mineral density status compared to age, ethnicity, and gender-matched controls (Purdy). The toxicity was mild in most but was possibly worse in smaller children taking higher doses of tenofovir and growth tended to recover once children stopped taking the drug.

"Higher tenofovir exposure in smaller children, who must take the adult formulation of the drug, because a paediatric formulation is not available, may also contribute to the degree of bone mineral density loss. Careful monitoring of HIV-infected children requiring treatment with tenofovir is warranted," the authors wrote.

Two other studies presented at the conference suggested that tenofovir passes the transplacental passage quite efficiently, though levels were lower in pregnant mothers during the third trimester than postpartum (Burchett, Bonora). Neither of these studies addressed safety to the foetus, however, pregnancy outcome data from the DART study (in which 70% of women are on tenofovir) suggest that so far, congenital abnormality rates appear similar to other studies (Namale). But at present, WHO guidelines recommend that tenofovir not be used in pregnant women if other options are available.

Drug interactions

Several drugs appear to have drug interaction with tenofovir. These include the PIs: lopinavir/ritonavir and atazanavir (which all increase tenofovir levels and may be associated with a slightly higher risk of tenofovir-related toxicity). Conversely, tenofovir may lower these PIs' minimum blood concentrations, particularly in treatment-experienced patients (Breilh 2004). When given with tenofovir, it is recommended that atazanavir be boosted with ritonavir.

When a person is taking tenofovir as well as other pharmaceutical drugs which are known to cause kidney toxicity, there may be an increased risk of renal side-effects. If co-administration with nephrotoxic drugs (e.g. ganciclovir, foscarnet, pentamidine, amphotericin, vancomycin, interleukin-2, cidofovir, or the aminoglycosides) cannot be avoided, weekly monitoring of renal function is recommended.

Co-administration with tenofovir results in increased concentrations of (and potentially life-threatening side effects from) ddI (Guo 2004; Martinez 2004; Moyle 2004b). Since the drugs may have antagonistic antiviral effects (and increase the risk of tenofovir-resistance), it would appear to be safer to follow Gilead's guidance and avoid the combination altogether.

Tenofovir resistance – and the implications for sequencing

Most of the data to date have suggested that tenofovir rarely selects for drug-resistant virus – usually occurring in less than 3% of patients, unless tenofovir is being administered with other nucleoside analogues that can also select for the K65R resistance mutation (such as ddI or abacavir) (Brandi) see <http://www.aidsmap.com/en/news/78EAD875-0630-454E-BF09-D8AA2F8F9B3.asp>. However, these data are derived from studies conducted in people infected with HIV-1B, and where people tend to have their regimens changed rather quickly in response to rising viral load results.

In resource-limited settings, it could be a whole other ballgame. For instance, some drug resistance mutations emerge at different frequencies and speeds in different viral subtypes.

Preliminary data from Botswana suggest that the K65R mutation may emerge more frequently in people infected with HIV-1C (the predominant clade of virus in Southern Africa, Ethiopia and India), especially those who have been on regimens containing ddI and d4T (Doualla-Bell, Brenner) (see

<http://www.aidsmap.com/en/news/900B4B14-A172-41D5-AA8F-C46B07BC2E9D.asp>.

Another study, from Dr Somnuek Sungkanuparph and colleagues in Thailand, showed that failure to detect virologic failure soon enough was associated with a high level (10%) of tenofovir-resistance – this time on patients failing on a fixed dose combination of d4T/3TC/nevirapine. In a multivariate analysis, log viral load at failure (OR 10.48; 95%CI 1.77 to 62.13, $p = 0.010$) and duration of ART prior to failure (OR 1.12; 95%CI, 1.03 to 1.21, $p = 0.008$) predicted the occurrence of tenofovir resistance.

This means that tenofovir-containing second-line regimens could be much less effective in countries with subtype C HIV epidemics.

Emergence of K65R may also be more frequent in settings where people are kept on failing treatment because of limited access to viral load monitoring. Preliminary resistance data from the DART trial in people on tenofovir plus *Combivir* out to 48 weeks suggest that while the K65R mutation may be relatively uncommon, it still occurred in 15% of the people with viral loads over 1000 copies/ml (Pillay). Other mutations, such as the 3TC resistance-conferring mutation M184V were far more common (up to 78%), possibly because AZT is believed to reduce the likelihood of K65R, but it was still much more frequent than what has been observed in developed countries. Researchers could detect no differences in patterns of emerging mutations between HIV-1 subtypes A, C, and D however – but this could have been the result of coadministering AZT with tenofovir.

This frequency of K65R implies that both abacavir and ddI, drugs reserved for second-line therapy in resource-limited settings, could be less effective in a substantial minority of patients.

So when should tenofovir be used?

In light of such findings, there should be considerable debate about when tenofovir-containing regimes should be used.

“I have always thought that tenofovir should be in the first line,” Dr Francesca Conradie of the University of the Witwatersrand Clinical HIV Research Unit told HATIP. “It has a low side-effect burden, is easy to take and preserves the thymidine analogues (either AZT or d4T) for the second-line.” (Until now, clinicians have had little choice but to use d4T or AZT after one another, which compromised the efficacy of the second-line regimens since the two thymidine analogues are largely cross-resistant.)

“The data on the selection of K65R selections in subtype C are worrying. If we do not use it first line it may be gone,” said Dr Conradie. “Perhaps the solution is to combine it with AZT and prevent the K65R. But I still think that first line is the place.”

How much will access really improve?

However, even though the approvals are welcome, clinicians such as Dr Conradie may still not be able to use the drug as she would like. In fact, it looks very likely that tenofovir-containing regimens will become even more difficult to access through the public sector in South Africa.

Dr Francois Venter, President of the South African HIV Clinicians Society and local HIV advocacy groups such as Treatment Action Campaign blame this on the cost of tenofovir and *Truvada*, which is currently far too expensive for the public sector programmes in most African countries (see

<http://www.aidsmap.com/en/news/9C80024F-7788-4F7E-BD98-9295268D1599.asp>).

At present, Aspen Pharmacare holds a voluntary license from Gilead Sciences to market each of these drugs in sub-Saharan Africa and has so far received regulatory approval to sell tenofovir or *Truvada* in a dozen or so other countries including Ghana, Zambia, Ethiopia, Uganda, Kenya, Malawi, Botswana, Namibia, Rwanda, Nigeria, the Democratic Republic of the Congo, Senegal, and Tanzania.

In many countries, including South Africa, there was previously limited access which permitted importation on compassionate use basis for those who had failed or were intolerant to other options. However, the paperwork was considered laborious by many overworked clinicians and getting the medication could take a few weeks, so that most patients who would have benefited from the treatment could not easily access it – though some did. In fact, some better resourced-South African patients found it simpler and faster to drive across the border and purchase *Truvada* at retail pharmacies in Namibia – though at considerable expense. At N\$420 (~US \$60) per month, *Truvada* costs three times the price of a one-month’s worth of efavirenz.

However, at that cost, approval in Namibia hasn’t meant dramatically improved access for the majority of patients there. Still following old versions of WHO guidelines, the combination is relegated to salvage therapy.

“Tenofovir is available for HAART in the public sector in Namibia since about one year for second line treatment; i.e. it is given when d4T substitution with AZT is not possible or if the patient has an hepatitis B infection, where tenofovir and lamivudine are indicated,” according to Karl F. Steinhausen, who is the pharmacist for the Antiretroviral Clinic in Keetmanshoop, Namibia. “Also in the new national guidelines that are in preparation, tenofovir will remain a second line medicine.”

For the time being, the same fate seems likely in South Africa, according to Dr Kevin Rebe of GF Jooste Hospital which serves the periurban communities of Cape Town: “Unfortunately I think that governments are going to be slower to take up *Truvada* into their

public protocols so it is unlikely to be freely available via government clinics for first line therapy for a while yet.”

The price tag is just one part of the problem however. The price at which *Truvada* is being sold at pharmacies across the country is actually quite similar to the price Aspen charges for its generic formulation of lamivudine/zidovudine (AZT/3TC), which at R341 (\$49) (VAT and dispensing fee inclusive) is about R50 (\$7) per month less than what GlaxoSmithKline charges for *Combivir*, and about 50 (\$7) more per month than what Cipla charges for its version of AZT/3TC.

Nevertheless, the price being charged in retail pharmacies does not prevent the government from negotiating a better price in the public sector as it has in the past for other drugs. Plus, the guarantee of a sizeable government order would allow the company to introduce economy of scale into the manufacturing process.

Doubtless a little competition for Aspen would be a good thing – and would reduce the risk of stock-outs.

But it could be that the guarantees associated with the government purchasing process are the other part of the problem. It’s a bit of a double-edged sword, really, as the South African government has already committed to buy large supplies of stavudine (d4T) which is cheap, but which is being abandoned in clinical practice in many countries because of the risk of serious long-term side-effects, such as lipatrophy, lactic acidosis and peripheral neuropathy. But the South African government has made its antiretroviral purchasing commitments through 2008 – and, without increased advocacy, practice in the public sector is unlikely to change until the next ARV tender is announced.

But whether government’s stock on hand or purchase orders should affect the care offered to people with HIV is a thorny dilemma.

Botswana has faced a similar problem in relation to second-line ART according to Dr Tendani Gaolathe of Infectious Disease Clinic at Princess Marina Hospital in Gaborone, speaking at the Botswana International HIV Conference last year.

“For our protease inhibitor (PI), the guidelines say *Kaletra*. But nelfinavir was our 2nd line drug in the first guidelines, and unfortunately, we still have so much in stock. We had more than we needed,” she said. “So then the question was, ‘do we really switch to *Kaletra*, or do we throw this nelfinavir away - what happens? Or should we use it up once our stocks are down and then move on to *Kaletra*?’ This is just one of the tough decisions we have to make when we consider issues of cost for these drugs, especially when we already have them in our stores. And what we will need to consider since access is free in this country: the cost implications of switching our guidelines when we have so many to treat.”

Fortunately, this problem does not involve many patients in Botswana. At the time of Dr Gaolathe’s talk last year, less than 5% of all patients in the National ART Programme were on the second-line regimen.

Still, continuing to use nelfinavir as the first PI in patients goes against the conventional wisdom and guidance in developed countries, because it is less effective than a boosted-PI, such as *Kaletra*, and because people who are exposed to and fail on a suboptimal PI could develop resistance mutations that reduce their chances of benefiting from subsequent PIs.

Likewise, the growing body of data (resistance and toxicity) are suggesting that the sequence in which tenofovir-containing regimens are used could be more important in non-Western settings than has previously been reported in developed countries – and procuring the best care for the population available should outweigh considerations of cost (within reason) or stock on hand.

References

- Bonora S et al. *Transplacental passage of tenofovir and other antiretrovirals at delivery*. Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 738a, 2007.
- Brandi C J et al. *Long-term follow-up of patients taking tenofovir DF with low-level HIV-1 viremia and the K65R substitution in HIV-1 RT*. AIDS 21: 761-763, 2007.
- Brenner BG et al. *Facilitated selection of K65R resistance with tenofovir pressure in subtype C HIV-1 isolates*. Fifteenth International Workshop on HIV Drug Resistance, Sitges, Spain, abstract 150, 2006.
- Burchett S et al. *Tenofovir pharmacokinetics during pregnancy, at delivery and postpartum*. Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 738b, 2007.
- Cassetti I et al. *The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) through five years in antiretroviral-naïve patients*. Eighth Congress on Drug Therapy in HIV Infection, Glasgow. Abstract P 152. 2006.
- Cheng A et al. *Safety profile of tenofovir DF in treatment-experienced patients from randomized, placebo-controlled clinical trials*. Fourteenth International AIDS Conference, Barcelona, abstract TuPeB4460, 2002.
- De Jesus E et al. *Effects of switching from fixed dose zidovudine/lamivudine to fixed dose tenofovir/emtricitabine: maintenance of virologic suppression and other benefits*. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, abstract H-517, Washington DC, 2005.
- Dore G et al. *Anti-hepatitis B virus (HBV) activity in HBV/HIV co-infected patients treated with tenofovir DF (TDF) and lamivudine (LAM) versus LAM alone: 144-week follow-up*. Fifteenth International AIDS Conference, Bangkok, abstract MoPeB3308, 2004.
- Doualla-Bell F et al. *High prevalence of the K65R mutation in human immunodeficiency virus-infected Batswana patients treated with ddI/d4T-based regimens*. Fifteenth International Workshop on HIV Drug Resistance, Sitges, Spain, abstract 46, 2006.
- Eliou R et al. *COL40263: resistance and efficacy of once-daily Trizivir and tenofovir DF in antiretroviral naïve subjects*. Eleventh Conference on Retroviruses and Opportunistic Infections, San Francisco, abs 53, 2004.
- Gallais H et al. *The Viread™ expanded access program (EAP) in Europe/Australia: summary of the safety and efficacy of tenofovir disoproxil fumarate (TDF) in antiretroviral treatment (ART) experienced patients*. Fifteenth International AIDS Conference, Bangkok, abstract TuPeB4552, 2004.
- Gallant JE et al. *Early non-response to tenofovir + abacavir and lamivudine in a randomized trial compared to efavirenz + abacavir and 3TC: ESS30009 unplanned interim analysis*. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, abstract H1722a, 2003.
- Gallant JE et al. *Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomised trial*. JAMA 292: 191-201, 2004.
- Gazzard B et al. *The combination of tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) has significantly greater response vs fixed dose zidovudine/lamivudine (CBV) and EFV in antiretroviral naïve patients: a 24 week preliminary analysis*. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, abstract H-1137C, 2004.
- Giacomet V et al. *12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children*. J Acquir Immune Defic Syndr 40: 448 – 450, 2005.
- Guo Y et al. *Fatal lactic acidosis associated with coadministration of didanosine and tenofovir disoproxil fumarate*. Pharmacotherapy 24: 1089-1094, 2004.
- Harris J et al. *Emtricitabine therapy for hepatitis infection in HIV-1 patients co-infected with hepatitis B: antiviral response and genotypic findings in antiretroviral treatment naïve patients*. Eleventh Conference on Retroviruses and Opportunistic Infections, San Francisco, poster 836, 2004.
- Kaleebu P on behalf of the DART trial. *48 week virological response to a triple nucleoside/nucleotide analogue regimen in adults with HIV infection in Africa within the DART trial*. Third International AIDS Society Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, abstract WeOaLB0203, 2005.
- Kearney P et al. *Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics*. Clinical Pharmacokinetics. 43: 595-612, 2004.
- Landman R et al. *Low genetic barrier to resistance is a possible cause of early virologic failures in once-daily regimen of abacavir, lamivudine, and tenofovir: the Tonus study*. Eleventh Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 52, 2004.
- Madruga R et al. *Switch from stavudine (d4T) to tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) resulted in continuing virological suppression and improvement in lipoatrophy though 2 years in HIV-infected patients*. Eighth Congress on Drug Therapy in HIV Infection, Glasgow. Abstract P 120. 2006.
- Madruga JVR et al. *Switch from stavudine to tenofovir DF in combination with lamivudine and efavirenz resulted in continued virologic suppression and improvement in lipoatrophy through 2 years in HIV-infected patients*. Eighth International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Francisco, poster 29, 2006.
- Martinez E et al. *Pancreatic toxic effects associated with coadministration of didanosine and tenofovir in HIV-infected adults*. Lancet 364: 65-67, 2004.
- McComsey G et al. *Alendronate with calcium and vitamin D supplementation is superior to calcium and vitamin D alone in the management of decreased bone mineral density in HIV-infected patients: results from ACTG 5163*. Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 42, 2007.
- Moyle G et al. *Unexpected drug interactions and adverse events with antiretroviral drugs*. Lancet 364: 8, 2004b.
- Namale L et al. *Pregnancy and pregnancy outcome among women in the DART trial*. Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 746, 2007.
- Neff GW et al. *Tenofovir therapy for lamivudine resistance following liver transplantation* (December). Ann Pharmacother (online edition), 2004.
- Nelson M et al. *An open-label study of tenofovir in HIV-1 and hepatitis B virus co-infected individuals*. AIDS 17: F7-F10, 2003.
- Pillay D et al. *Emergence and evolution of drug resistance in the absence of viral load monitoring during 48 Weeks of Combivir/Tenofovir within the DART trial*. Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 642, 2007.
- Purdy J et al. *Tenofovir DF salvage therapy in HIV-infected children and further studies on bone mineral density*. Fourteenth

Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 720, 2007.

Rey D et al. *Early virologic non-response to once daily combination of lamivudine, tenofovir and nevirapine in antiretroviral naïve HIV-infected patients: preliminary results of the DAUFIN study.* Fourteenth Conference on Retroviruses and Opportunistic Infections, Los Angeles, abstract 503, 2007.

Rey D et al. *Virologic response of zidovudine, lamivudine, and tenofovir disoproxil fumarate combination in antiretroviral-naïve HIV-1-infected patients.* JAIDS 43 (5): 530-534, 2006.

Ristig MB et al. *Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus – coinfecting individuals for whom interferon-alpha and lamivudine therapy have failed.* Journal of Infectious Diseases 186:1844-1847, 2002.

Rousseau F et al. *Emtricitabine (FTC): HBV DNA viral load assessments over 36 weeks in patients with chronic HBV infection.* Eighth Conference on Retroviruses and Opportunistic Infections, Chicago, abstract 55, 2001.

Schooley R et al. *Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study.* AIDS 16(9):1257-1263, 2002.

Sheldon J et al. *Genotypic changes in HBV-DNA of HBV/HIV co-infected patients after long-term exposure to tenofovir.* 44th Interscience Conference of Antimicrobial Agents and Chemotherapy, Washington, DC, abstract V-1154, 2004.

Squires K et al. *Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial.* Ann Intern Med 139: 313-320, 2003.

Sungkanuparph S et al. *Tenofovir resistance among HIV-infected patients failing a fixed-dose combination of stavudine + lamivudine + nevirapine in a resource-limited setting.* Fourteenth Conference

on Retroviruses and Opportunistic Infections, Los Angeles, abstract 663, 2007.

Tarantal AF et al. *Administration of 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) to gravid and infant rhesus macaques (Macaca mulatta): safety and efficacy studies.* J Acquir Immune Defic Syndr Hum Retrovirol 20: 323-333, 1999.

Tarantal AF et al. *Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta).* J Acquir Immune Defic Syndr 29: 207-220, 2002.

Towner W et al. *Efficacy of a once daily (QD) regimen of nevirapine (NVP), lamivudine (3TC) and tenofovir (TDF) in treatment-naïve HIV infected patients: a pilot study.* Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract P49, 2004.

van Böel F et al. *Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection.* Hepatology 40: 1421-1425, 2004.

Wang LH et al. *Pharmacokinetic and pharmacodynamic characteristics of emtricitabine support its once daily dosing for the treatment of HIV infection.* AIDS Research and Human Retroviruses. 20(11):1173-1182, 2004.

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