An Open Letter to John Kearney, CEO of GlaxoSmithKline, South Africa

President Mbeki's directive on 28 October 1999 that the safety of your AIDS drug AZT be investigated on the basis that 'there is a large volume of scientific evidence ... that [AZT] is harmful to health' alerted the South African public to the fact that AZT is dangerously toxic. Which shouldn't have surprised anyone, since it was synthesised in 1961 and tried out for a couple of years thereafter as an experimental cell poison. The reams of horrible medical literature to which the President was referring are summed up in my little book *Debating AZT: Mbeki and the AIDS drug controversy* (*). But apart from being lethal to all cells it reaches, your company is sitting on an even darker secret about AZT: It doesn't work. It cannot and does not have the antiretroviral effect you claim for it. Here's why.

You allege in the package insert supplied with AZT that it's converted by enzymes inside human cells from its parent form as a pro-drug into its active agent, AZT triphosphate. And that AZT triphosphate stops HIV replication by being incorporated into growing proviral DNA chains during reverse transcription of HIV RNA. But neither of these claims is true and your company knows it.

In November 1986 Furman and others including researchers from Wellcome Research Laboratories (a division of your company in an earlier incarnation) reported their finding in *Proceedings of the National Academy of Sciences of the United States of America* 1986; 83: 8333-7 that the minimum concentration of AZT triphosphate necessary to inhibit proviral HIV DNA chain synthesis significantly, i.e. have an antiretroviral effect, is 0.7μM. That's in the most ideal artificial conditions *in vitro*, never mind the much tougher

real world *in vivo*, in which a massively higher intracellular concentration of the drug would be necessary.

In your company's rush to market the drug in 1987, after ramming it through FDA approval following completely botched and corrupted clinical trials, it didn't bother ascertaining whether the cells of people given AZT are able to triphosphorylate it to that level. Thirteen subsequent investigations all returned findings revealing that they are unable to do so, no matter what the dose. Or to be more precise, that they do so at utterly negligible levels, with the best executed studies of the lot reporting AZT to be triphosphorylated *in vivo* at levels one, even two orders of magnitude below the minimum effective concentration that Furman *et al* reported necessary for the drug to work as a nucleoside analogue reverse transcriptase inhibitor.

Would you please explain then why you claim that 'Zidovudine [AZT] is phosphorylated in ... cells to ... the triphosphate (TP) derivative', by implication to effective virustatic concentrations *in vivo*, when study after study has consistently shown that it isn't?

If AZT prevents HIV replication by terminating proviral HIV DNA chain synthesis as your package insert alleges, one would expect AZT ingestion to result in a consistent, sustained and simultaneous fall over time in all direct markers conventionally considered to indicate HIV infection levels – namely HIV DNA (viral burden), HIV RNA (viral load), detection of p24 and reverse transcriptase (viral isolation) and p24 antigenaemia. But all reported studies of the effect of AZT on these parameters show that the drug has no such anti-HIV effect. None at all on HIV DNA synthesis (viral burden), which flatly refutes your key claim that the drug blocks it. An entirely insignificant effect on HIV RNA (viral load). And none on the rest. All of which is perfectly

predictable since AZT isn't triphosphorylated by our cells anywhere near sufficiently to block HIV retrotranscription, as we've seen.

So why do you claim that 'Zidovudine-TP acts as an inhibitor of, and substrate for, the viral reverse transcriptase', that 'The formation of further proviral DNA is blocked by incorporation of zidovudine-TP into the chain and subsequent chain termination (*sic*)', and that AZT is thus 'an antiviral agent ... active against ... HIV', when all investigations of the effect of AZT on HIV infection levels *in vivo*, measured by direct markers, have exposed these claims as untrue?

The studies are surveyed and discussed, together with the triphosphorylation data, in an explosive 30,000-word review of the molecular pharmacology of the drug by Papadopulos-Eleopulos *et al*, published in mid-1999 as a special supplement to *Current Medical Research and Opinion* Vol. 15 (#). You were given a copy a couple of months after it came out. You've never responded to it.

Why too do you claim that AZT is 'effective', when the only long term, large scale, prospective, randomised, double-blind, clinical AZT study yet conducted – the Concorde trials in England, Ireland and France, involving 1749 symptom-free HIV-infected individuals – found that AZT has no therapeutic benefits when administered early (*Lancet* 1994; 343:871-81), and the extended results of the study a year later showed 'a significant increased risk of death among the patients treated early' (*New England Journal of Medicine* 1997; 336:958-9)?

The families and other survivors of the thousands of people poisoned by AZT would love to know. Their lawyers too, I'm sure. Because your continued

marketing of AZT as an anti-HIV drug in the face of all these findings, with sales of AZT and 3TC topping $1.1 billion last year alone, looks like a colossal fraud. Or at least like the kind of gross negligence that had the directors of drug-maker *Chemie Grunenthal* filing into a criminal dock after Thalidomide.

In your reply addressing the triphosphorylation and efficacy issues that I've raised, you can leave out the effect of AZT on T4 (CD4+) cell counts and on antibody levels. These are indirect non-specific markers modulated by cell poisons like AZT independently of any antiviral activity. Best keep mum about AZT and 'mother to child transmission'. There's a Pandora's Box of horrors you'd do well to keep closed. And if you don't mind, please spare us the 'AZT has brought quality of life to AIDS sufferers around the world' spiel. The one your company pumped with part of its $4.7 billion general marketing budget last year. Save it for the widow and young son of a legal colleague of mine who in good health embarked on a course of AZT and 3TC treatment on the strength of your company's promises, immediately took very ill on it, and then steadily wasted to a skeleton in diapers with his muscle and gut tissue poisoned off, uncontrollably vomiting his life away into a bucket.

Thanks.

ANTHONY BRINK
PIETERMARITZBURG
26 April 2001

Ps: Table setting out the triphosphorylation data, and a graph plotting the effect of AZT on viral load herewith.

- **Debating AZT: Mbeki and the AIDS drug controversy* can be […] read online at: www.tig.org.za
- *# A Critical Analysis of AZT and its Use in AIDS* by Papadopulos-Eleopulos *et al*, *Current Medical Research and Opinion* Volume 15 (Special supplement) is posted online at: www.tig.org.za

[Hyperlinks updated]

TRIPHOSPHORYLATION OF AZT *IN VIVO*.

Year	Peak Concentration of Triphosphorylated AZT Reported	Reference
1991	0.5 pmol/10^6 cells	Kuster H, et al. *J Infect Dis*; 164: 773 – 776
1991	56 pmol/10^7 cells (5.6 pmol/10^6 cells)	Toyoshima t, et al. *Analytical Bioch*; 196: 302 – 307
1992	0.14 pmol/10^6 cells	Slusher JT, et al. *Antimicrob Agents & Chemoth*: 2473 – 2477
1994	326 fmol/10^6 cells (0.326 pmol/10^6 cells)	Robbins BL, et al. *Antimicrob Agents Chemother*: 115 –121
1994	0.06 pmol/10^6 cells	Barry MG, et al. *AIDS*; 8: F1 – F5
1996	95 fmol/10^6 cells (0.095 pmol/10^6 cells)	Rodman JH, et al. *J Infec Dis*; 174: 490-499
1996	0.069 pmol/10^6 cells	Peter K, et al. *J Pharm & Biomed Anal*; (14): 491 – 499
1996	0.042 pmol/10^6 cells (average)	Peter K and Gambertoglio JC. *Clin Pharmacol Ther*; 60: 168 – 176
1996	0.07 pmol/10^6 cells	Barry MG, et al. *AIDS*: 1361 – 1367
1998	0.046 pmol/10^6 cells, in mononuclear cells from lymph nodes. 0.085 pmol/10^6 cells, in PBMC	Peter K et al. *AIDS*: 1729 –1731
1998	160 fmol/10^6 cells (average) (0.16 pmol/10^6 cells)	Fletcher CV, et al. *Clin Pharmacol Ther* 64: 331 – 338
1998	0.07 pmol/10^6 cells	Robbins BL, et al. *Antimicrob Agents Chemother*: 2656 – 2660
1999	193 fmol/10^6 cells (0.193 pmol/10^6 cells)	Font E, et al. *Antimicrob Agents Chemother*: 2964-8

1μmol = 10^{-6} moles
1 fmol = 10^{-15} moles
1 pmol = 10^{-12} moles
1 pmol/10^6 cells=1 μM

1 mole (mol) is a quantity of 6.02 x 10^{23} molecules
1 micromolar (μM) is a concentration of 1 micromole (μmol) per litre.

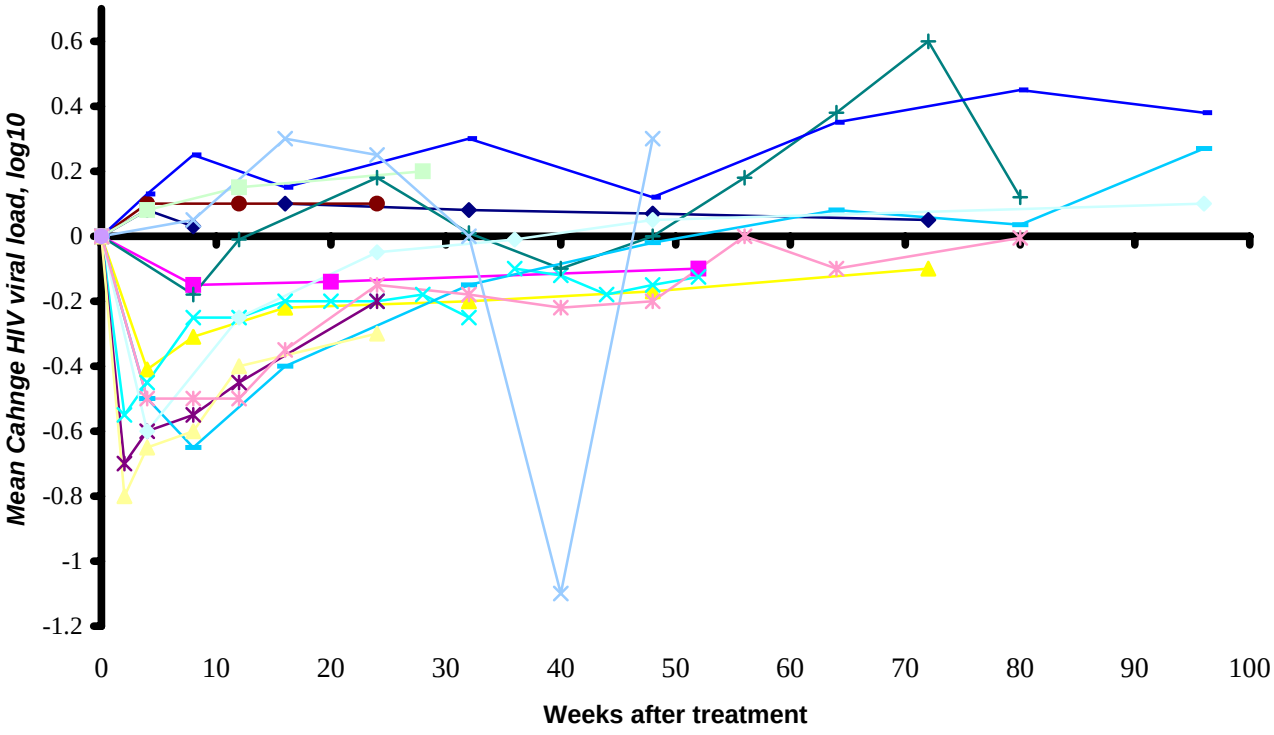
Changes of HIV viral load induced by AZT

1. According to American HIV experts Saag, Shaw and Coombs and their associates in their article *HIV viral load markers in clinical practice* in *Nature Medicine* 1996; 2(6): 625-9: 'A three-fold or greater sustained reduction (>0.5 log) of the plasma HIV RNA levels is the minimal response indicative of an antiviral effect... [R]eturn of HIV RNA levels to pre-treatment values (or to within 0.3-0.5 log of the pre-treatment value), confirmed by at least two measurements, is indicative of drug failure'.

2. According to the 1997 British HIV Association guidelines for antiretroviral treatment published in The Lancet 1997; 349:1086-1092: 'If the viral load has not fallen by about 1 log 8-12 weeks after treatment initiation consideration should be given to modify therapy'.

3. All studies in which the effect of AZT on HIV viral load in patients has been investigated, have consistently established that AZT taken alone or in combination with other drugs is not able to induce a sustained decrease in the 'plasma HIV RNA level' of >0.5 log (the American criterion for anti-HIV drug efficacy), much less 1 log (the British criterion).

4. By both the American and British criteria mentioned above, AZT fails to achieve 'the minimal response indicative of an antiviral effect' and is therefore a 'drug failure' *i.e*. ineffective as an antiviral drug against HIV.



(a.) Carr A, et al. *AIDS*, 1996:635-641; (b.) Katlama C. et al. *JAMA*, 1996:118-25; (c.) Staszewski S, et al. *JAMA*, 1996:111-117; (d.) Delta Committee. *AIDS*, 1999:57-65; (e.) Lillo F. *AIDS*, 1999:791-6; (f.) Bakshi SS, et al. *J Infect Dis* 1997:1039-50; (g.) Bruisten SM, et al. *AIDS Res & Hum Retr* 1998:1053-8; (h.) De Jong MD, et al. *PNAS* 1996:5501-6; (i.) Katzenstein D, et al. *NEJM* 1996:1091-8; (j.) Eron JJ, et al. *NEJM* 1995:1662-9; (k.) O'Brien WA. *NEJM* 1996:426-31.