POISONING OUR CHILDREN
AZT and nevirapine in pregnancy

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For further copies of Poisoning our Children telephone or email us, or print it off our TIG website. If you have any suggestions as to other individuals or groups likely to share your concern about the latest AZT and nevirapine foetal toxicity findings discussed in this dossier – and what they predict for the health and well-being for generations of South Africa’s future young, mostly black, mostly poor – we’d be grateful if you would pass their contact/mailing details on to us.
Preface

What do you do if ... university people, professors and scientists ... haven’t read ... won’t read? What do you do?

President Thabo Mbeki
Sunday Times 6 February 2000

Just over five years ago, on 28 October 1999, after reading an early draft of my book manuscript Debating AZT: Questions of safety and efficacy (later published as Debating AZT: Mbeki and the AIDS drug controversy*), President Thabo Mbeki made an extraordinary announcement in Parliament:

There ... exists a large volume of scientific literature alleging that, among other things, the toxicity of this drug [AZT] is such that it is in fact a danger to health. These are matters of great concern to the Government as it would be irresponsible for us not to heed the dire warnings which medical researchers have been making. I have therefore asked the Minister of Health ... to go into all these matters so that ... we ourselves, including our country’s medical authorities, are certain of where the truth lies.

Since it was – still is – almost universally believed that AZT is both safe and effective in preventing mothers from infecting their babies with HIV, and the government had been under intense pressure to spend billions on buying it for this purpose, President Mbeki’s statements ignited a local and international furore. ‘The President has been gravely misinformed,’ protested AZT manufacturer GlaxoWellcome (now GlaxoSmithKline) – and AIDS doctors, treatment activists and journalists everywhere agreed, all expostulating indignantly about how very irresponsible he was to make these statements.

Taking no account of key research papers reporting the serious toxic effects of AZT, nor an explosive critical analysis of the molecular pharmacology of the drug just published in a leading academic medical journal*, the Medicines Control Council (MCC) disgracefully botched the enquiry that President Mbeki ordered, and suggested that he’d raised a false alarm.

A few months later, however, the demand on the government to supply AZT to pregnant women switched to nevirapine instead – another exceptionally toxic drug. Citing the results of a single study in Uganda, HIVNET 012 – a scandalous mess – credulous AIDS doctors, activists and journalists took to trumpeting that one magic-bullet dose of nevirapine given to a woman in labour and then to her newborn baby
could protect the child being infected by its mother. So why, they all complained angrily, was the government dragging its heels by running a cautious pilot study, and not dishing it out to every HIV-positive pregnant woman showing up at public hospitals to give birth, and to her baby too, without further ado?

The professional drug lobbyists and earnest AIDS doctors, cheered along by all the media, took their demands to court in 2001, and got a judge to force the government to ditch its UN-AIDS approved pilot study and to prescribe nevirapine from his bench to all HIV-positive mothers labouring in public hospitals and to their newborn babies, ordering the government to supply the drug for this purpose. Why, the manufacturer was even offering it free. (For a while – like any savvy drug dealer.)

In May 2002, the day before the government’s appeal against this order, the MCC publicly announced that it was reviewing its special provisional registration of nevirapine for use in maternity wards, in view of the fact that a few weeks earlier Boehringer Ingelheim had withdrawn its application to the Food and Drug Administration in the US for a similar licence, after the emergence of what the FDA described as ‘potentially quite serious problems’ with the conduct of the HIVNET 012 nevirapine trial. Entirely unfazed by this development, the learned justices of the Constitutional Court unanimously dismissed the government’s appeal in July – never mind that HIVNET 012 had been the lynchpin of the entire case. (Part Five of the writer’s essay The trouble with nevirapine* tells how one of their lordships got so stuffed on the moral meal they made of it that, tired and emotional afterwards, he actually burst into tears.)

The time for the formation of an organized group to counter the TAC’s propagandizing, politicking and merchandizing for the pharmaceutical industry in South Africa was well overdue. In November, at a convention meeting a hotel in Johannesburg, the Treatment Information Group was founded. The meeting was followed by another in Cape Town several months later, but my professional situation in the Eastern Cape at the time was a practical hindrance, and it was only when I settled in Cape Town in 2004 that we were able to get going.

In 2003, after finally falling in with the FDA and rejecting HIVNET 012 too, our MCC put nevirapine manufacturer Boehringer Ingelheim on terms to come up with some other evidence that the drug is safe and effective – allowing its continued administration to women in labour and their babies in the meanwhile, without any support for this in the medical literature. But at least keeping the treatment activists’ tempers cool.

This is where we come in. The six-month period that the MCC afforded the drug company to justify the continued special registration of nevirapine for perinatal use had long come and gone when on 22 June
2004 we wrote our first letter to the MCC enquiring how it was getting along with its review. The MCC’s stupefying response on 12 July was to issue a statement that it no longer supported the use of nevirapine taken solo – but that it now recommended that pregnant women henceforth be given AZT as well.

With this announcement, the MCC took us back to square one. Not only was it still countenancing the use of AZT in pregnancy, it was now actively recommending that it be given to pregnant women in South Africa, mostly black, mostly poor, in the teeth of many more serious foetal toxicity reports published in the medical literature since President Mbeki sounded the alarm in 1999.

The Cabinet responded with a statement on 21 July noting the MCC’s ‘pronouncement ... on problems of resistance in the usage of nevirapine as a monotherapy in preventing mother-to-child transmission of HIV’, and recording that ‘The Department of Health is reviewing the information in order to make a recommendation to Cabinet on the future course of action, taking into account information demonstrating that combined antiretroviral therapy is more effective and less risky. In the meantime, nevirapine monotherapy will be provided in public hospitals as is currently the practice, ensuring that mothers are given all the necessary facts so they can make an informed choice.’

Our second letter highlighted the illogic of the MCC’s new position on nevirapine, and criticised its support for the use of AZT in pregnancy in view of the published toxicity literature concerning the drug. Our third and fourth letters covered our submission of the seminal AZT pharmacology analysis by Papadopulos-Eleopulos et al., mentioned above, along with another extensive paper by the same authors, the writer now included, *Mother to Child Transmission of HIV and its Prevention with AZT and Nevirapine: A Critical Analysis of the Evidence*, exposing the whole shambles, neither of which papers the MCC’s members had bothered to read, apparently. Our fifth letter corrected a date error.

But it’s the research findings concerning the demonstrated dangerous toxicity of AZT for unborn and newly born babies discussed in depth in our sixth, seventh, ninth and tenth letters that we expect you’ll find really shocking – after which we’ll be surprised if you disagree with the observation in our eighth letter that ‘having regard to the corpus of published AZT toxicity data drawn to Council’s attention in our correspondence, we propose that any of its members still recommending the prescription of AZT to pregnant women and their newborn babies, mostly black, mostly poor, [must be] ignorant, lazy, simple, corrupt or depraved’.
Far from being ‘more effective and less risky’, as the MCC led the Cabinet to believe, you’ll soon appreciate that the MCC’s recommendation of AZT in combination with nevirapine in pregnancy exposes thousands of South African children, mostly black, mostly poor, to death, serious disease, immunological disorders, brain damage and other organ damage and/or sub-clinical but serious neurological injury from transplacental and post-natal poisoning.

And although the Cabinet was concerned that ‘mothers are given all the necessary facts so they can make an informed choice’, you can bet your last cent that none of the toxic injury findings canvassed in our letters will be communicated to African women being urged by AIDS doctors to swallow these chemicals while pregnant and to allow them to be squirted in syrup down their newborn babies’ throats. Because let’s be realistic: if they were, how many of them would agree to it?

The look of it is that, faced with the horrible research data we have brought to their attention in our letters, the small clique of anonymous, secretive, unaccountable pharmaceutical industry sweethearts on the MCC sub-committee responsible for this appalling new recommendation will not have the brains, the integrity or the courage to reverse their blunder, because a public climb-down is going to be professionally humiliating – and difficult too, considering the pervasive influence of the pharmaceutical industry at our medical school campuses, where the MCC’s decision-making ‘external consultants’ teach and busy themselves with research funded by lavish drug company grants.

At the University of Cape Town, for instance, where medical academics have been particularly vocal in supporting the use of antiretroviral drugs in pregnancy, their dean is on Merck’s payroll via a front foundation that it funds, ECI; GlaxoSmithKline has endowed a professor’s chair; and need we say more about UCT’s Boehringer Ingelheim Lung Institute? Just for starters.

If you’re in politics or human rights advocacy, press for the public disclosure of the identities of the drug industry cronies who recommended that pregnant women in South Africa, mostly black, mostly poor, be given AZT, and for a thorough public airing of their direct and/or indirect financial ties to the pharmaceutical industry. Call them to account; make them explain on record, on oath, in the public eye, how they can be recommending that AZT be given to African pregnant women and their newborn babies, knowing how harmful it is. This, you’ll read, is now abundantly and incontestably established by peer-reviewed research findings, some very recent, published in the world’s leading medical and scientific journals, and summarised in our letters – so the MCC can’t say ‘We never knew’ anymore, as its members have been telling Dr
Tshabalala-Msimang in their private phone calls to her since receiving them. Telling her too that they had been ‘amazed’ by our ‘detailed research’ of the toxicity literature, of which they’d been ‘unaware’. Well, obviously.

If you’re in the media, publicize these research findings, following the heroic lead of your tenacious and fearless colleagues four decades ago. As John Braithwaite recounted in Corporate Crime in the Pharmaceutical Industry (Routledge & Kegan Paul, 1984), ‘Investigative journalists played a more important role than health regulatory authorities in many parts of the world in saving children from thalidomide.’ Recalling Chemie Grunenthal’s indifference to his desperate efforts in November 1961 to persuade the German drug company to stop marketing thalidomide in view of the deformities it was causing, Dr Widukind Lenz confirmed that ‘the drug was withdrawn, largely due to reports in the press’. After that drug disaster, doctors promised that never again would children be poisoned in their mothers’ wombs. How many children in South Africa, mostly black, mostly poor, need to be killed or injured by ‘antiretroviral’ drugs before doctors remember?

A letter from MCC Chairperson Professor Peter Eagles, dated 22 November 2004, referring to our first two letters only, informed us that the MCC had engaged an ‘independent expert’ to consider them. Our reply mentioned (a) some breaking news from Associated Press about the deliberate, fraudulent suppression by top officials in the US National Institutes of Health of adverse findings concerning the safety of nevirapine and AZT for African babies, and (b) a massive retrospective study, just published, confirming that AZT and other antiretroviral drug treatment of pregnant women leads to ‘a very high neonatal mortality rate’ among their babies.

Nearly a year later, on 28 October 2005, Eagles wrote to say no worries, these drugs are fine. This is dealt with in the afterword of this book, along with the latest research findings on how ARV drugs harm the unborn.

The medical research finding canvassed in these letters are summed up in two statements that I made in the Mail & Guardian on 26 November 2004, in an article under the heading ‘Why should South Africans continue to be Poisoned by AZT’:

- Hundreds of studies have found that AZT is profoundly toxic to all cells of the human body, and particularly to the blood cells of our immune system.
- Numerous studies have found that children exposed to AZT in the womb suffer brain damage, neurological disorders, paralysis,
Knowing better, the Treatment Action Campaign’s standing big-time ‘AIDS expert’, Professor Robin Wood, co-director of the Desmond Tutu HIV Centre at the University of Cape Town, responded in the newspapers and in court papers claiming that:

the toxicity of [AZT and similar drugs] is very low indeed … Children exposed to AZT in the womb are not at high risk of ‘brain damage, neurological disorders, paralysis, spasticity, mental retardation, epilepsy, other serious disorders and early death’. The opposite is true. When AZT is used by a pregnant woman to reduce the risk of transmitting HIV to her child, the child is much less likely to contract HIV and much more likely to live a healthier, longer life.

After reading the medical research findings about this canvassed in these letters, particularly in the sixth, you’ll be well placed to decide who’s the ignorant bozo.

On the defensive over its advocacy of nevirapine in the light of Associated Press’s revelations in mid-December (reviewed in Part Nine of *The trouble with nevirapine*), the Treatment Action Campaign has reaffirmed that AZT is its ‘drug of choice’ for pregnant women. Responding to the Associated Press reports on behalf of fellow AIDS doctors, Dr Ashraf Coovadia, pediatric HIV clinic chief at Johannesburg’s Coronation Mother and Child Hospital, expressed the same medical consensus. What ‘the Rolls Royce’ of AIDS drugs, as he calls AZT, does to unborn and newly born children is the principal subject of this book.

Please act to prevent this impending atrocity in South Africa.

ANTHONY BRINK
CONVENOR AND NATIONAL CHAIRMAN:
TREATMENT INFORMATION GROUP
Cape Town
1 December 2005

*See: www.tig.org.za*
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22 June 2004

THE REGISTRAR: MS PRECIOUS MATSOSO
MEDICINES CONTROL COUNCIL
2nd Floor, Hallmark Building
Cnr Andries and Vermeulen Streets
Pretoria

Dear Ms Matsoso

MCC Review of Special Registration of Nevirapine for Perinatal Administration

We would like to pose several questions to Council concerning the status of its pending review of its special registration of nevirapine as an anti-HIV perinatal prophylactic drug. Before we do, it might assist if we recapitulate the history of the review to date:

1. On the basis of findings reported from HIVNET 012, a clinical trial in which the efficacy of perinatally administered nevirapine to prevent mother to child transmission of HIV was investigated, Council provisionally approved the drug for this novel indication in March 2001 – taking the lead as the first developing country in the world to do so. (Nevirapine has never been licensed for perinatal use in any first world nation.)

2. On 16 March 2002, in view of what the US Food and Drug Administration described in a press statement as ‘potentially quite serious’ data integrity problems that it had discovered with HIVNET 012, Council notified National Minister of Health Dr Tshabalala-Msimang by letter that ‘We are to review nevirapine in the light of these developments and will inform you of the decision as soon as information is available.’

3. On 22 March 2002, Boehringer Ingelheim withdrew its application to the FDA for a licence to market nevirapine as a perinatal anti-HIV prophylactic in the US.

4. On 4 May 2002, Council made a public announcement confirming that its special registration of nevirapine as a perinatal anti-HIV prophylactic drug was under review.

5. In April 2003, the US National Institutes of Health, which had sponsored and participated in HIVNET 012, delivered a final report to Council, in which it identified several basic problems with the study –
concluding nonetheless: ‘In summary, the re-monitoring of the study determined that nevirapine, 200mg orally given to the mother at delivery and 2mg/kg given to the neonate within 72 hours, is safe and effective. However the conduct of the study lacked the necessary documentation to support a request to the FDA to consider this study as a stand alone pivotal trial.’

6. In short, notwithstanding the fatal deficiencies of HIVNET 012 as a pivotal licensing trial by US drug licensing standards, the NIH contended that the study proved the safety and efficacy of perinatally administered nevirapine for ‘a developing country’ (per final NIH report).

7. Council naturally disagreed with the NIH’s implication that a double standard should apply in its assessment of the drug’s efficacy and safety for South African babies, and on 25 July 2003 resolved to ‘reject the study HIVNET-012 as a pivotal study for the approval of the use of Nevirapine for the reduction of risk of intrapartum transmission of HIV-1 infection’, and to put nevirapine manufacturer Boehringer Ingelheim on terms ‘to submit in 90 days any new evidence (other than previously submitted evidence on HIVNET-012 and SAINT information) to convince the MCC of retention of this indication’.

8. Council based its reasons for rejecting HIVNET 012 on findings recorded in the NIH’s final report on it, namely that: patient records did not support the published results; there were problems with the manner in which the study was conducted; records did not account for how the drug was stored, handled and distributed; records indicating which treatments were allocated to trial participants were missing; and the obtaining of voluntary informed consent for the trial participants could not be confirmed in all cases.

9. In other words, Council found HIVNET 012 to have been irredeemably compromised by radical data integrity defects and by fundamental problems with the manner in which the trial was conducted, which vitiated any conclusions drawn from it.

10. It bears emphasizing that it was the preliminary findings of HIVNET 012 that gave rise to the Treatment Action Campaign’s complaint against the state ‘for not providing nevirapine to every HIV positive pregnant woman and babies born to HIV positive mothers’ and that founded its successful case in the High and Constitutional Courts for a mandamus directing it to do so. The effect of this order was that the state was compelled to abandon its UNAIDS-sanctioned pilot studies of perinatal nevirapine (UNAIDS director Peter Piot had recommended in the New York Times on 11 July 1999 that it was ‘unrealistic to introduce it on a large scale in developing counties without first using pilot programs’) and was ordered to provide nevirapine to women in labour and their new-born
babies ‘on a large scale’ without further preliminary testing for safety and efficacy. (HIVNET 012 itself had been an unconvincingly small study, with only about a third of the originally intended number (1500) of mother-child pairs enrolled in it (645), just under half of whom were assigned to the nevirapine wing – an unconvincingly small cohort for a clinical drug trial intended to serve as the basis of a licensing application.)

11. In giving its reasons for rejecting HIVNET 012, however, Council took no account of a plethora of even more fundamental flaws in the design, execution and interpretation of the study, discussed in *Mother to Child Transmission of HIV and its Prevention with AZT and Nevirapine* by Papadopulos-Eleopulos et al., a 170 000-word monograph submitted to the Department of Health in November 2001, amplified by *A Critical Analysis of the Evidence Considered Proof that Nevirapine Prevents Mother-To-Child Transmission of HIV*, a PowerPoint slide presentation prepared by the same authors (both accessible at www.theperthgroup.com), and further canvassed in Professor Sam Mhlongo’s 100-point submission, *Issues Concerning Perinatal Nevirapine Treatment* (copy annexed), a formal synopsis (as at August 2002) of the writer’s polemic *The trouble with nevirapine* (posted at www.openbooks.co.za), delivered to Council on 6 August 2002, and acknowledged by Council’s Director of Clinical Evaluation and Trials, Dr Rajen Misra, by telephone two days later. Nor was any account taken of the neonatal toxicity considerations canvassed in Dr Roberto Giraldo’s paper, *Scientific Data Against the Use of Nevirapine in Pregnant Women, Infants, Children, and Anybody Else*, submitted to the Department of Health via Ministerial advisor Dr Ray Mabope in October 2001 (posted at www.robertogiraldo.com).

12. On 5 September 2003, purporting ‘to clarify the intention of this resolution’ (to reject HIVNET 012 and require extrinsic evidence to ‘convince the MCC of retention of this indication’), Council recalled it, and substituted it with a second one, in which it reiterated its rejection of ‘HIVNET 012 as a pivotal study’ and required Boehringer Ingelheim ‘within six months of this resolution’ to present ‘data that you have in your possession, or which you are in a position to obtain ... demonstrating the efficacy of Nevirapine’, alone or in combination with other antiretroviral drugs, as a perinatal anti-HIV prophylactic.

13. The following day, on 6 September 2003, the HIVNET 012 research team published a second report on the study in *Lancet* – heralded by an extraordinary and unprecedented simultaneous press release by the US State Department, puffing the second report under the headline, *Findings could help prevent 800,000 annual infections.*
14. A week after putting Boehringer Ingelheim on terms to demonstrate the efficacy of perinatally administered nevirapine, Council issued a press statement of 12 September 2003, in which it stated that ‘Nevirapine has been shown to be effective in reduction of the risk of intrapartum transmission of HIV-1 infection from mother to child. Scientific evidence was provided to the MCC to support this’.

15. However, Council’s categorical statement concerning the allegedly freshly demonstrated perinatal efficacy of the drug was contradicted by a tentative statement in the same press release concerning the origin of the ‘scientific evidence’ in question – identified as comprising ‘additional data from South African researchers ... that may support the continued use of Nevirapine for this indication’ (our emphasis).

16. Council further referred to ‘additional information regarding the original study [that] has also now been published’. (In fact, the second HIVNET 012 report was only published in *Lancet* the following day, but presumably Council was given sight of the paper in proof.)

17. Council concluded in its statement: ‘Recognizing the importance of the new information, the MCC, on 5 September 2003, adopted a new resolution, which extends the time period for Boehringer Ingelheim (the supplier of nevirapine) to review existing evidence, and to submit additional data for expert assessment by the MCC.’

18. According to a report in the Health Systems Trust bulletin *Healthlink* on 19 September 2003, the ‘additional data from South African researchers’ comprised findings in studies conducted at Chris Hani-Baragwanath and Coronation Hospitals.


20. In ‘The pathologist who struck gold’, published in the Spring/Summer 2001 issue of *Hopkins Medical News*, lead author of the second HIVNET 012 report, Professor J Brooks Jackson restated one of the trite, elementary requirements of a meaningful clinical drug trial:

> No researcher can assess a drug’s effectiveness with scientific certainty without testing it against a placebo. That’s the only way we can know for sure if a short course of AZT or nevirapine is better than nothing.

**QUESTION ONE:** Are we correct in assuming that by ‘data ... demonstrating the efficacy of Nevirapine’ (to quote the language of its second resolution), Council envisaged that such ‘data’ would be clinical
trial findings of sufficient cogency as to support the special registration in question – in other words (to quote the language of its first resolution), that the ‘data’ would amount to a ‘pivotal study for the approval of the use of Nevirapine for the reduction of risk of intrapartum transmission of HIV-1 infection’, that is, the kind of study that would meet the criteria and standards for efficacy and safety for this special indication set by first world drug regulatory authorities such as the US FDA, the European Agency for the Evaluation of Medicinal Products (EMEA) and the Therapeutic Products Programme of Health Canada?

QUESTION TWO: Have any of these ‘additional data from South African researchers’, to which Council referred in its press statement of 12 September 2003, been published in a peer-reviewed journal, and if so when and where?

QUESTION THREE: Were the clinical trials conducted at Chris Hani-Baragwanath and Coronation Hospitals, that gave rise to ‘additional data from South African researchers’, placebo-controlled?

QUESTION FOUR: Have the findings in these local studies been deemed sufficiently cogent to serve as pivotal support for the special registration of nevirapine as a perinatal anti-HIV prophylactic in any other country of either the first or developing world?

QUESTION FIVE: Has Council determined whether these new ‘additional data from South African researchers’ do indeed ‘support the continued use of Nevirapine for this indication’ and that, to quote Professor Jackson, they do so ‘with scientific certainty’?

QUESTION SIX: Having regard to Council’s unequivocal rejection of the HIVNET 012 researchers’ preliminary findings reported in *Lancet* on 4 September 1999, does Council share the US Administration’s conclusion asserted in the headline of its press statement that the second report on the study, published on 6 September 2003 in the same journal, establishes that nevirapine administered perinatally prevents mother to child HIV infection?

QUESTION SEVEN: Indeed, having rejected HIVNET 012 on the grounds that it was radically flawed, rendering all data produced from it insecure, does Council accord any significance to the second HIVNET 012 report whatsoever, and if so, on what basis?

QUESTION EIGHT: Precisely what ‘additional data’ did Boehringer Ingelheim ‘submit ... for expert assessment by the MCC’ in the six-month period that Council allowed it on 5 September 2003 to support the ‘retention’ of its special licence to market nevirapine for administration to HIV-positive women in labour and their new-born babies?
QUESTION NINE: If in reviewing its special registration of nevirapine as a perinatal anti-HIV prophylactic, Council (a) abides by its resolution to reject HIVNET 012 *in toto*, and (b) considers that none of the ‘additional data from South African researchers’ constitutes a ‘pivotal study for the approval of the use of Nevirapine for the reduction of risk of intrapartum transmission of HIV-1 infection’, for the reason that the studies at the South African hospitals in question were not placebo-controlled (and/or for any other reason), and so do not establish the ‘drug’s effectiveness with scientific certainty’ (to quote Professor Jackson), what is delaying Council’s immediate deregistration of nevirapine for this special indication?

QUESTION TEN: In the situation, does Council accord itself with the estimation expressed by Supreme Court of Appeal Judge Edwin Cameron in an interview on the MNet programme Carte Blanche on 4 November 2001 that ‘nevirapine is a very good drug ... to give to mothers who are about to have babies’ and to the babies themselves shortly after their birth, and that the state’s concern that the safety and efficacy of the drug for babies first be established in local pilot trials ‘is a tragedy I think’ – and if not, why, almost four months since the expiry of the time allowed Boehringer Ingelheim to ‘submit additional data for expert assessment by the MCC’, are South African babies, overwhelmingly African, still being exposed to this extremely poisonous chemical without any justification for it in the medical research literature?

We suggest that there is some urgency to the determination of Council’s pending review of its registration of nevirapine for perinatal administration for the following reasons:

(a) Nevirapine is a dipyridodiazepinone compound characterised by Boehringer Ingelheim in its package insert as a chemotherapeutic agent. It is an exceptionally dangerous drug, having what the company describes in detailed warnings in the insert as ‘severe, life-threatening’ toxicities, notably to the liver and epidermal tissue – summarised and emphasized in special hazard notices set in boxed, bold typeface against conspicuous highlighted grey backgrounds, as required and approved by Council on 14 April 2000 when the drug was approved for adult ingestion. On information supplied by Boehringer Ingelheim, the *Physicians’ Desk Reference* similarly emphasizes the toxicity of nevirapine in a lengthy paragraph, whose text is set in upper case throughout.

(b) In view of the caveat in the *Physicians’ Desk Reference* that ‘Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis ... has occurred in patients treated with Viramune’ (nevirapine), the company advises that ‘Clinical chemistry tests, which include liver function tests,
should be performed prior to initiating Viramune’. (Due to the failure of Council to issue guidelines in this regard, such tests, even though mandated by the manufacturer to avoid toxic tort liability, are not routinely conducted before the administration of nevirapine to South African women in labour and to their babies.)

(c) Notwithstanding the prominent toxicity warnings in the inserts packaged with nevirapine in Europe and the US, continuing reports of serious adverse reactions to nevirapine in the form of **SEVERE AND LIFE-THREATENING CUTANEOUS AND HEPATIC REACTIONS** (to quote the European EMEA), some fatal, moved the EMEA and US FDA to issue special urgent alerts about this in April and November 2000 respectively.

(d) For the reason mentioned in a report in the *New York Times* on 5 January 2001 – ‘nevirapine can produce liver damage severe enough to require liver transplants, and has caused death in such use, the Centers for Disease Control and Prevention said in its weekly report’ – the US CDC proscribed nevirapine on 5 January 2001 for even short-term administration to medical professionals suffering needle-stick injuries on the advice of the US FDA, following numerous reports of acute toxic reactions fielded by its monitoring arm MedWatch.

(e) All chemotherapeutic drugs have potent cytotoxic activities and are particularly hazardous for neonates, for the reasons noted by Haddad et al. in their text, *Clinical Management of Poisoning and Drug Overdose* (WB Saunders, 1998):

> The physiology of the newborn is unique [in the manner in which ‘drugs are absorbed, distributed, metabolized and excreted’], and organs that have an important role in susceptibility to and the moderation of toxic reactions, such as the liver and kidney, are immature in their function. As a result, the manner in which the neonate handles a toxic exposure is frequently quite different from the response of an older child or adult.

(f) Babies are consequently incomparably much more susceptible to the effects of toxic drugs than adults, so reducing an adult dose of a dangerous drug per body weight for a baby – as is the practice with neonatal nevirapine treatment – does not result in a correlative risk of drug-injury or fatality.

(g) It is universally recognised current medical policy to avoid or minimise foetal and neonatal exposure to harmful or potentially harmful chemicals, because it has become notorious that early exposure to such agents can have severe long-term health-damaging consequences, often only presenting clinically in later life.
(h) Nevirapine was pointedly omitted from the US CDC’s latest revised guidelines for interventions to prevent mother to child transmission of HIV published on 17 March 2002, which is to say that American AIDS experts do not consider the drug safe and effective for administration to American women in labour and their newborn babies.

(i) A recent query to the US FDA’s Division of Drug Information in March 2004 by Dr Valendar Turner of the Department of Health, Western Australia, concerning whether nevirapine is approved for the treatment of mothers and their newborn babies to prevent mother to child transmission of HIV in the US, drew a categorically negative reply:

Viramune is not FDA approved for the prevention of HIV in mother-to-child transmission, by itself or in combination with other drugs. If used in this fashion, it would be an off-label use. Viramune is FDA approved for HIV infected, pediatric patients 2 years and above. It is not approved for use in the newborn at their time of birth to prevent whatever HIV is transmitted from the mother establishing itself as infection in the newborn.

(j) The first report of HIVNET 012 in Lancet recorded that

The rate of serious adverse events in the two groups [of babies] was similar up to the 18-month visit (19.8% in the zidovudine group, 20.5% in the nevirapine group), with the median age at last visit being 183 days ... The most frequent cause of serious adverse events within 56 days of birth were sepsis, pneumonia, fever, congenital anomaly, asphyxia, and dyspnoea. [Eighteen babies suffered maculopapular rash, and twenty-two anaemia.] The frequency and severity of laboratory-detected toxic effects, including neutropenia, thrombocytopenia, and abnormalities in creatinine or bilirubin, were similar in the two groups. ... 38 babies (6.8%) died (22 (7.9%) in the zidovudine group, 16 (5.7%) in the nevirapine group). The most frequent causes of death were pneumonia, followed by gastroenteritis, diarrhoea, dehydration and sepsis.

(k) Although only clinically healthy mothers were accepted into HIVNET 012, almost six per cent of their babies treated with nevirapine died.

(l) Even the strikingly high one-in-five incidence of serious adverse events among babies following nevirapine administration appears to have been under-reported: a press statement by the NIH on 22 March 2002 revealed that there had been ‘professional differences of opinion’ between the American researchers and the Ugandan hospital staff concerning what constituted a ‘serious adverse event’.
(m) The HIVNET 012 researchers cautioned in their first report that ‘long term follow up of the babies remains a high priority to find out about possible long-term toxic effects’. In other words, without having first conducted conventional animal studies to determine the safety of nevirapine administration to neonates, the researchers were unperturbed by the ethical implications of conducting an open-ended medical experiment on African children to ‘find out’ whether they might be seriously and permanently injured by nevirapine’s ‘possible long-term toxic effects’.

(n) It is apparent from their second report that whether the children treated with nevirapine suffered ‘possible long-term toxic effects’, perhaps sub-clinical in some cases, was not a matter given any close attention.

(o) The likelihood that a dose of nevirapine will have significant toxicity for human neonates is predicted by the Physicians’ Desk Reference’s note that prenatal exposure in rodent studies resulted in ‘significant decrease in fetal body weight’.

(p) One of the serious possible ‘long-term toxic effects’ of dosing neonates with nevirapine that the HIVNET 012 researchers did not entertain was its effect on neonatal brain development, particularly having regard to the note in the Physicians’ Desk Reference that ‘Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.’

(q) The neurotoxicity of nevirapine was noted in the British Medical Journal on 13 April 2002: Wise et al. reported Neuropsychiatric Complications Of Nevirapine Treatment in three cases in which adults attempted suicide following the development of ‘delirium, an organic affective state, and an organic psychosis’ evidenced by ‘low mood ... cognitive impairment and clouding of consciousness ... impaired consciousness ... visual hallucinations ... persecutory delusions and depressive thoughts’. The psychologists found that the ‘nevirapine treatment was clearly related to the evidence of symptoms’.

(r) The particular vulnerability of neonates to neurotoxic chemicals is illustrated by the hexachlorophene debacle in the middle decades of the 20th century, in which an antiseptic in the dioxin class that was considered safe for inclusion in soap and talc for decades, with which babies used to be routinely washed and powdered after birth, was banned in the US in 1976 for inclusion in such products when it was finally identified as the cause of epileptic seizures and death among new-born babies – thirty-four at a Parisian Hospital in 1972. Subsequent infant autopsies and animal experiments confirmed the chemical’s activity as a nerve poison. (A six-year investigation published in 1978 found that nurses who routinely
washed their hands with hexachlorophene solutions had borne an
extraordinarily high number of deformed children.)

(s) The risk that South African babies, born to mostly poor Black
mothers, might suffer ‘possible long-term toxic effects’ from even a
single dose of a drug as extremely poisonous as nevirapine administered
shortly after birth cannot be underestimated – even if the percentage
harmed might be low. Thalidomide, the most notorious pharmaceutical
drug catastrophe in the modern era provides an object-lesson in this
regard, albeit that the toxic drug exposure in question occurred earlier in
the child’s development. Goth recounts in Medical Pharmacology
(Mosby, 1984, 9th ed.):

The piperidinedione hypnotic thalidomide was responsible for
thousands of children with disastrous defects such as absence of
limbs. ... Pregnant women ingesting a single hypnotic dose of the drug
between the twenty-fourth and thirty-sixth day of their pregnancy
have delivered severely deformed babies.

Having regard to how many thalidomide doses were ingested (taken alone
or combined with aspirin and other drugs it was briefly a best-seller) it is
noteworthy that the incidence of physical deformity was relatively rare:
only about twenty thousand babies born deformed in the West. (No tally
exists of babies killed in the womb – or of children crippled in developing
countries.) As President Mbeki correctly pointed out in his letter to Judge
Cameron on 15 March 2000: ‘Undoubtedly, such “consensus” and
“available evidence” [reflecting Cameron’s language] also existed on the
use of thalidomide’. Between 1958 and 1962, relying on the
manufacturer’s assurance that thalidomide ‘can be given with complete
safety to pregnant women and nursing mothers without adverse effect on
mother or child. ... a harmless, safe and effective sedative with no side
effects. ... Harmless even over a long period of use ... completely
harmless even for infants ... Outstandingly safe’, doctors in turn
effusively extolled the drug to pregnant women as both safe and effective.
It is noteworthy that it was public and political pressure, and not medical
reaction to the sudden spate of physical deformities, that led Chemie
Grüenthal and British Distillers (Biochemicals) to withdraw the drug.

(t) Not only newborn babies are at dire risk from exposure to nevirapine;
according to a report in the Mail & Guardian in April 2002, a single dose
administered to a woman in labour proved fatal.

(u) Since the Physicians’ Desk Reference pertinently warns that ‘the
safety profile of Viramune in neonates has not been established’, whether
South African children suffer liver and other organ damage, and or brain
damage and/or impairment – perhaps initially sub-clinical and only
apparent in later years – on account of their exposure to nevirapine as
babies will be only be evident in time, that is when Boehringer Ingelheim’s experiment upon them is complete. Another drug calamity serves as a precedent for the baleful potential in this regard:

(v) Hundreds of thousands of women were medically advised to take the synthetic hormone diethylstilbestrol (DES) in the nineteen-fifties and sixties, advertised by its manufacturer ‘for routine prophylaxis in ALL pregnancies ... 96 per cent live delivery with desPLEX in one series of 1200 patients – bigger and stronger babies, too. No gastric or other side effects with desPLEX – in either high or low dosage.’ Thousands of women exposed to diethylstilbestrol in utero developed ordinarily very rare clear-cell adenocarcinoma of their vaginas and cervixes in adulthood, and suffered structural changes in their reproductive organs (virilization), causing infertility, ectopic pregnancies, miscarriages, and preterm labour and deliveries. The damage caused by the drug only became evident decades after administration.

(w) It is indeed so that expert medical opinion in South Africa strongly supports the continued use of nevirapine in maternity wards. In a striking departure from the basic principles of evidence-based medicine, local experts unanimously condemned Council’s decision to reject the corrupt HIVNET 012 data. For instance, Professor Jerry Coovadia, Professor of HIV/AIDS Research at the Nelson Mandela School of Medicine, University of Natal called it ‘unscientific and downright perverse. ... I think this is just such a dreadful mistake.’ Eighteen members of the executive committee of the Health Sciences faculty at the University of Cape Town issued a public protest:

Deregistering nevirapine on unscientific grounds will be a devastating blow to our evolving Aids prevention programme and will be morally and ethically indefensible. If the council has any evidence to suggest that nevirapine is indeed toxic or not effective, then they should make such information available immediately. If not, they should refrain from creating the belief in the minds of the public that this proven and effective treatment is useless or even harmful.

Dr Keith Bolton, chairman of the South African Paediatric Association opined equally frantically:

I am convinced that millions of lives would be lost if this bungle is allowed to happen. ... The executive committee of Sapa believes the efficacy and safety of Nevirapine usage, as part of a strategy for the prevention of transmission of HIV from mother to child, has been adequately established beyond reasonable doubt. We believe that failure to continue to administer Nevirapine at this time would constitute a dereliction of the ethical duties of individual health care
professionals as well as an unconstitutional abdication of responsibilities of our health authorities. ... We urge our members in the field to follow their conscience by utilising the accepted practice of providing Nevirapine as part of the PMTCT programme. In doing so they will dramatically and significantly lower the risk of transmission of HIV from mother to child and thus prevent most cases of childhood Aids.

Yet another drug disaster, undoubtedly the worst in the history of medicine, is instructive here:

(x) As late as 1939, the 24th edition of *Hale-White’s Materia Medica: Pharmacy, Pharmacology and Therapeutics* was still expressing the expert medical consensus that mercury is ‘one of the most valuable medicines we have. ... Children take mercury very well.’ Any doctor today prescribing mercury – ranked by the University of Tennessee’s renowned Toxicology Center near plutonium as one of the most poisonous substances known to man – in even the smallest amount to anyone for whatever reason, would be probably be struck from the medical roll for dangerous professional incompetence. As a guide to deciding good drugs from bad ones – both useless and extremely dangerous – the prevailing expert medical consensus has consistently failed us.

(y) It will be recalled that the HIVNET 012 researchers ascribed all the deaths of drug-treated babies in their study to HIV infection. No doubt similar conclusions are being drawn by South African doctors administering nevirapine under the country’s judicially ordered perinatal treatment programme when nevirapine-exposed babies fail to thrive, fall ill or die. Certainly this was the experience reported by people gravely harmed by nevirapine combined with other AIDS drugs in the local FTC 302 trial, aborted by order of Council in April 2000 after several fatalities: approached by injured trial-subjects, doctors conducting the study discounted the extreme toxicity symptoms they were suffering to the onset of AIDS.

(z) In 1554, in his textbook *Universa Medica*, French physician Jean Francois Fernel had already observed that nearly all the symptoms of tertiary syphilis (distal gangrene, paralysis and dementia before death) were really due to mercury poisoning. Yet four centuries later, the 13th edition of *Black’s Medical Dictionary* published in 1936 was still recommending: ‘In syphilis, mercurial preparations are very extensively used, and must be taken by the subjects of this disease over many months in order to render a cure likely.’ The tendency of medical practitioners to ascribe the toxic ill effects of their treatments to microbes, especially
those to which their imaginations are in thrall in their particular era, is evidently an enduring one.

Might we expect your replies within the next fourteen days? Please confirm by return.

Yours faithfully

ADV ANTHONY BRINK
CONVENOR AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP

Postscript: This enquiry takes no account of manifestly spurious claims by provincial health officials published on the front-page of the Star on the 8th instant under the headline, ‘Nevirapine has in three years saved nearly 58 000 newborn babies in Gauteng from contracting HIV and AIDS’.

Annexure ‘A’

Issues concerning perinatal nevirapine treatment

Unanswered submission to the MCC on 6 August 2002

1. The US Food and Drug Administration (FDA) licensed nevirapine on 21 June 1996 in terms of an accelerated ‘fast-track’ licensing procedure, without a conventional full assessment of its safety and efficacy.

2. Boehringer Ingelheim’s licence application to the FDA was based upon an indication that in combination with the nucleoside analogue drugs, AZT and ddI, nevirapine might possibly have some therapeutic value.

3. This indication derived solely from the effect of a triple combination of the said drugs on a single surrogate marker for antiretroviral activity, CD4 cell counts.

4. Nevirapine alone had no effect on CD4 cell counts, and combined only with AZT, the effect was negative.

5. The FDA’s licence granted to Boehringer Ingelheim (BI) was provisional only.

6. Confirmation of the provisional licence was dependent upon BI conducting further clinical studies and demonstrating that the drug has clinical benefits i.e. improves quality of life and or extends life.

7. The provisional licence for nevirapine was furthermore subject to restrictive conditions concerning marketing and prescription,
inasmuch as the FDA approved the supply of the drug in combination with nucleoside analogue drugs only, and not for prescription solo.

8. Nevirapine was approved for use only in adults demonstrating clinical and/or immunological deterioration.

9. BI was granted provisional licences subject to similar conditions by the European Agency for the Evaluation of Medicinal Products (EMEA) on 5 February 1998 and by the Therapeutic Products Programme (TPP) of Health Canada on 17 September 1998.

10. Before the grant of a provisional, conditional licence in Canada, nevirapine had twice been rejected by the Canadian TPP due to ‘an absence of scientific evidence of efficacy and ... concerns about safety’.

11. The TPP in Canada continues to have ‘outstanding concerns about efficacy associated with this drug’.

12. To date, BI has yet to demonstrate to the FDA, the EMEA or the TPP that the administration of nevirapine has any clinical benefits.

13. Accordingly, the licences granted in all these jurisdictions remain provisional and have still to be confirmed.

14. High rates of severe hepatic and dermatological toxicities, all life threatening and some fatal, led the EMEA and the FDA to issue special safety alerts about nevirapine in April and November 2000 respectively.

15. On account of its severe toxicity, nevirapine is categorised by the EMEA in its register of approved drugs for prescription only to persons with ‘pronounced immunological and/or clinical deterioration’ – in other words, as drug of last resort.

16. On 5 January 2001 the US Centers for Disease Control (CDC) contraindicated the administration of nevirapine even for short term administration as an anti-HIV prophylactic to medical workers suffering needle-stick injuries, in view of reports fielded by MedWatch (the FDA’s drug toxicity reporting system) of the drug’s life-threatening acute hepatic toxicity, in at least one case requiring liver transplant, after an average of just two weeks of nevirapine treatment.

17. Nevirapine is a chemotherapeutic drug, and is categorised as such by its manufacturer Boehringer Ingelheim (BI).

18. All chemotherapeutic drugs have significant cytotoxic activities.
19. It is not conventional to administer chemotherapeutic agents to pregnant women or neonates, in view of their known hazards.

20. Because neonates are incomparably more susceptible to drug toxicity than adults, reducing an adult dose of a dangerous drug per body weight for a neonate does not result in a correlative reduction of risk level for drug-injury or fatality. In Clinical Management of Poisoning and Drug Overdose (WB Saunders, 1998), Haddad et al. sum up: ‘The physiology of the newborn is unique [in the manner in which ‘drugs are absorbed, distributed, metabolized and excreted’], and organs that have an important role in susceptibility to and the moderation of toxic reactions, such as the liver and kidney, are immature in their function. As a result, the manner in which the neonate handles a toxic exposure is frequently quite different from the response of an older child or adult.’

21. BI claims that ‘nevirapine binds to reverse transcriptase’ and that ‘eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine’.

22. The implication of these claims is that nevirapine specifically inhibits the retrotranscription of HIV RNA, does not inhibit cellular DNA formation, and is harmless to human cells.

23. BI’s implicit claims about the specific antagonism of nevirapine for HIV are indefensible, given that (i) reverse transcriptase is not unique to retroviruses, and is a component of uninfected human cells; (ii) the extreme cellular toxicity of nevirapine has manifested in numerous ‘severe and life-threatening’ ill effects, ‘including fatal cases’.

24. In other words, whatever its notional, potential antiviral activity in vivo, nevirapine has known profound general human systemic toxicity, presenting in a broad range of dangerous ill effects, as set out in extensively detailed warnings in the nevirapine package insert approved by the South African Medicines Control Council (MCC) on 14 April 2000. These severe toxicity warnings are summarised and emphasized in special hazard notices set in boxed, bold typeface against conspicuous highlighted grey backgrounds.

25. BI has yet to show that nevirapine has any antiviral activity in vivo: ‘The relationship between in vitro susceptibility of HIV-1 to nevirapine and the inhibition of HIV-replication in humans has not been established’ and ‘At present there are no results from controlled clinical trials evaluating the effect of VIRAMUNE in combination with other antiretroviral agents on the clinical progression of HIV-1 infection, such as the incidence of opportunistic infections or survival.’
26. The MCC granted a provisional licence to BI to supply nevirapine for administration to HIV-positive pregnant women in January 2001.

27. The basis of BI’s application to the MCC for a licence to supply nevirapine for this particular indication was a single study reported in *Lancet* on 4 September 1999, *Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial*.

28. BI, represented by Kevin Dransfield BS, participated directly in the conduct of HIVNET 012.

29. Following publication of the HIVNET 012 report, BI successfully relied upon it to win licences in numerous developing countries for the supply of nevirapine as a perinatal anti-HIV prophylactic.

30. BI is currently promoting nevirapine by way of ‘donations’ in these countries to establish its future market.

31. Nevirapine is not licensed for perinatal administration in the US, Europe or Canada, or in any other First World country.

32. Relying solely on the results of HIVNET 012, BI applied to the FDA for an extended licence to market nevirapine as a perinatal anti-HIV prophylactic.

33. When the FDA called for the production of the original 645 medical case files in HIVNET 012 for examination and auditing, in order to process BI’s licence application based on the study, the trial overseers were unable to produce them.

34. On 3 April 2002 the Kampala *Monitor* reported Professor Geoffrey Mmiro of Mulago Hospital in Kampala, one of the Ugandan overseers of HIVNET 012, stating that he had only been able to locate 100 of the files that the FDA had called for.

35. The unavailability of the files and the consequent inability of the FDA to review the conduct of HIVNET 012, and the integrity of its reported data, stymied the processing of the extended licence application, and on 22 March 2002 BI withdrew it accordingly.

36. The ‘potentially quite serious’ problems with HIVNET 012, as FDA spokesman Jason Brodsky described them in the press, went beyond the missing original case files and the consequent unverifiability of the researchers’ efficacy claims, in that John LaMontagne, Deputy Director of the National Institute of Allergy and Infectious Diseases (NIAID), a branch of the National Institutes of Health (NIH) of the US Department of Health and Human Services, revealed further in a press statement that there were often ‘differences of professional
opinion’ between the American and Ugandan researchers, concerning the incidence of serious toxic reactions among mothers and babies given a single dose of nevirapine.

37. The researchers’ claim in the report of the study that nevirapine apparently ‘seemed safe’ is rendered insecure by these frequent ‘differences of professional opinion’ about the incidence and gravity of toxic reactions, revealed by LaMontagne, but not mentioned in the trial report.

38. The data reported by the HIVNET 012 researchers founding their conclusions about the safety of perinatal nevirapine administration is accordingly compromised and cannot be relied upon for drawing any conclusion at all, other than that the safety of perinatal nevirapine remains moot.

39. The missing medical case files renders the ‘differences of professional opinion’ in the critical matter of the safety of nevirapine for pregnant women and their babies impossible to resolve.

40. Unless and until all the original case files are produced for auditing, the FDA will not accept the trial overseers’ reported claims about either the safety or the efficacy of nevirapine in perinatal situations.

41. The original records appear no longer to exist, given that LaMontagne claimed in press statements that ‘[There are] differences in the way hospitals in Uganda keep records and the requirements of the FDA’, which, ‘quite rightly has a rigorous standard’ and that the records will need to be ‘reconstructed’. This contradicts Mmiro’s allegation that the missing files are ‘stacked up in a container due to the ongoing rehabilitation at the hospital’. LaMontagne also made the claim, contradicting both Mmiro and himself, that the files are scattered over three different sites – Seattle, Baltimore and Uganda i.e. by implication, still exist.

42. NIAID’s interest in defending HIVNET 012 derives from the fact that NIAID researchers (Fowler, Miotti) participated in the conduct of the trial, and NIAID sponsored its cost. Other US federal health officials from the NIH (Mofenson) and the HIVNET Statistical Center (Fleming, Deseyve, Emel) also participated. To the extent that the American government was directly involved in the study and paid for it, considerable prestige is at stake, thus accounting for La Montagne’s less than forthright statements concerning the fatal trouble with the study.

43. On the basis of HIVNET 012, and its endorsement by NIAID, the World Health Organisation (WHO) recommends the perinatal administration of nevirapine in the Third World.
44. The negative ramifications of the missing source data for the integrity of the study, on the basis of which the WHO supports perinatal nevirapine treatment, are obviously very far-reaching.

45. Although only clinically healthy pregnant women were accepted into the trial, approximately seven per cent of the drug-exposed babies reportedly died.

46. The strikingly high mortality rate among treated babies does not support the conclusion that nevirapine administered perinatally ‘seemed safe’ for them.

47. Since there was no placebo wing to the study, it was not possible to make a relative mortality comparison, and the tentative conclusion that nevirapine ‘seemed safe’ for babies has no proper foundation accordingly.

48. No controlled, blinded epidemiological study has ever been performed anywhere in the world to establish the mortality rate among children born to HIV-positive mothers versus HIV-negative mothers, and consequently, fatal nevirapine toxicity is an equal contender with any other speculative cause for the seven per cent death rate noted among treated babies.

49. The conclusion that the drug ‘seemed safe’ is also irreconcilable with the fact that 80 per cent of clinically healthy mothers exposed to a single dose of nevirapine suffered ‘clinical or laboratory abnormalities’ (not specified in the report), twenty per cent developed viral or bacterial infections, 15 per cent parasitic infections, 13 per cent anaemia and about 5 per cent severe adverse events. Given the well-established acute toxicity of nevirapine, the aforementioned data support a conclusion contrary to the one reported, namely, ‘No adverse event was definitely or probably related to the study drugs.’ It is trite that patients exposed to chemotherapeutic agents risk greatly increased susceptibility to infections. The absence of placebo and untreated cohorts in the study for comparative purposes renders the reported conclusion invalid, or at minimum merely unsupported opinion.

50. In April 2002 the Mail & Guardian reported a case of a pregnant South African black woman killed by a single dose of nevirapine. [Erratum: she was killed by combination of ARV drugs; see ‘Death of an activist’.] 

51. Nevirapine was officially identified as the likely cause of death in at least two of the several fatalities that occurred in 2000/2001 among women on the FTC 302 trial conducted at Kalafong Hospital, Pretoria.
52. LaMontagne’s press statement that nevirapine is ‘a very, very safe drug’ is inconsistent with its widely and officially recognised serious toxicity profile, and is insupportable.

53. Based upon LaMontagne’s press statements, the assertions of the WHO and other bodies that there is no cause to question the safety and efficacy of nevirapine for perinatal administration, notwithstanding BI’s withdrawal of its extended licence application to the FDA, are *a fortiori* equally vacant and indefensible.

54. The short- and mid-term safety of nevirapine for babies remains unascertained.

55. The HIVNET 012 researchers themselves recommended that the long-term effect of exposing a baby to nevirapine should be researched, and to date it remains unknown.

56. LaMontagne’s press statement that ‘There is no question that the drug works’ is inconsistent with the fact that the majority of the original HIVNET 012 case files are missing, *ipso facto* placing the trial overseers’ efficacy claims for perinatal nevirapine administration in question in the view of the FDA.

57. The HIVNET 012 researchers failed to observe a single one of the essential prerequisites for a valid clinical drug trial, as reflected in the original protocol drawn for the conduct of the trial.

58. It was not blinded.

59. It was not placebo-controlled.

60. It contained no untreated cohort (neither on test drug, nor placebo, the importance of which has been stressed by the CDC).

61. It comprised a little over a third of the originally intended number of trial subjects, thus greatly reducing the statistical cogency of its results.

62. It was not properly randomised, inasmuch as two distinct testing protocols for determining HIV infection among pregnant women were reported: On one hand, subjects for the study were drawn from pregnant ‘women attending antenatal clinics at Mulago Hospital in Kampala, Uganda ... screened for HIV-1 infection by EIA [ELISA] for HIV-1 antibody. If a woman tested positive, she received post-test counselling about her infection status and was informed about the opportunity to enrol in HIVNET 012’. In other words, women reactive to a single ELISA HIV antibody test were diagnosed HIV-infected, told so, and invited to enrol in the trial. However the next sentence of the report states: ‘Women were eligible for the study if: they ... were positive on EIA and western blot for HIV-1 antibody.’
63. AIDS experts in the First World universally agree that a single reactive ELISA HIV antibody test result is an inadequate basis upon which to make a diagnosis of HIV infection, and require confirmation by follow-up testing.

64. Subsequent negative or indeterminate western blot test results exclude a significant number of reactive ELISAs.

65. ‘13 839 [women were] tested for HIV-1. 2144 [were noted as] with positive HIV-1 test. 1499 [were] excluded [i.e. about 70 per cent]. 645 mothers randomised.’ In other words, about 70 per cent of women ‘told of their infection status’ on the basis of a ‘positive HIV-1 test’ were excluded, among whom were an unreported number with negative or indeterminate western blot test results.

66. The necessary conclusion is that an unknown number of women who were ‘told of their infection status’, and were ‘counselled’ accordingly because they had a ‘positive HIV-1 test’, were not infected.

67. It is impossible to establish from the report how many women ‘with positive HIV-1 test’ and ‘told of their infection status’, who participated in the study, were enrolled without a western blot test performed on them.

68. It is similarly impossible to tell how many would have been negative or indeterminate upon subsequent western blot testing.

69. In any event, a positive western blot for ‘HIV antibodies’ itself does not in fact establish or confirm HIV infection: The specificity of HIV antibody tests, be they ELISA or western blot, has never been established by reference to the gold standard of HIV isolated from patient blood plasma by purification and electron photomicrograph verification; the positive predictive value of such tests is impossible to compute without knowledge of the prior probability of infection, based on the infection rate of the ‘risk group’ to which the patient belongs (determined by some other testing method); antibodies are inherently polyclonal and frequently exhibit as much if not a higher affinity for antigens other than those that putatively generated their production; and all the proteins employed in antibody tests, assumed by AIDS experts to be uniquely constituent of HIV, are demonstrably cellular, not retroviral – the necessary corollary being that high levels of ‘HIV antibodies’ detected by ELISA and western blot tests are actually auto-antibodies to endogenous human proteins, or antibodies to common mycobacterial and fungal organisms.

70. The possibility that uninfected women entered the trial corrupted it completely and vitiated its conclusions.
71. The HIVNET 012 researchers employed RNA-based qualitative and quantitative assays manufactured by Roche Diagnostics to diagnose and confirm HIV infection in babies, in contravention of the manufacturer’s express prohibitions against such uses, in view of their unknown specificity, thereby rendering meaningless the transmission rate data reported in the study.

72. The only RNA-based HIV assay approved by the FDA for use in clinical settings in the US is Roche Diagnostics’s quantitative RNA assay, licensed for determining ‘viral load’ only – after HIV infection has been established by way of antibody testing.

73. In terms of its current AIDS surveillance definition, the CDC inexplicably permits the use of RNA assays for determining mother-to-child HIV transmission in babies (but not infection via contaminated blood transfusion or any other source).

74. The CDC has stated that it supports such use of the assay for ‘surveillance purposes’ only, and not for making a ‘clinical diagnosis’.

75. The CDC has been unable to explain how and why RNA-based assays, too non-specific even for anonymous blood screening, and consequently prohibited for diagnosing and confirming HIV infection in adults and children, could and would be accurate and reliable for neonates infected by their mothers at birth or by breast feeding, but not by other means; nor has it been able to explain why an RNA-based assay should be good for determining mother-to-child HIV infection for surveillance purposes, but not clinical purposes, and why there should be any difference (since a baby is either infected or it isn’t, and if the test is unreliable for one purpose, it can’t be reliable for another).

76. Neither Roche Diagnostics nor the FDA permit the exception allowed by the CDC.

77. The HIVNET 012 researchers’ other basis for confirming HIV infection, namely the simple fact of neonate death without regard to the actual cause, be it pneumonia, gastroenteritis, diarrhoea, dehydration, sepsis (as reported), or toxic drug reaction (acute, or leading to the development of these conditions) was manifestly incompetent.

78. The extent to which the trial results were further corrupted by illegitimately treating neonate death per se as confirmation of HIV infection, as suggested by an experimental qualitative RNA test, cannot be determined because the report does not provide the figures.
79. Although the HIVNET 012 researchers stipulated that absolute prerequisites for the efficacy of perinatal nevirapine administration were reduction of maternal viral load, alternatively, attaining virustatic concentrations in neonates, nevirapine failed on both scores in the trial: It neither reduced maternal viral load, nor did the doses given attain *in vivo* inhibition concentrations (IC50) in any child. (Apparently ignorant of the IC50 of nevirapine *in vivo* as determined by Havlir et al. in 1995, the HIVNET 012 researchers arbitrarily picked a notional *in vivo* value for their clinical trial ten times the *in vitro* value originally determined by BI – but orders of magnitude below the *in vivo* value determined by Havlir et al.)

80. The HIVNET 012 researchers’ positive claims for perinatal nevirapine efficacy are irreconcilable with the fact that neither prerequisite for perinatal efficacy of nevirapine was met in the trial.

81. The foundational assumption made by the HIVNET 012 researchers in proposing the experimental administration of nevirapine at the onset of labour was that ‘Most vertical transmission occurs during active labour because of maternal blood transfusions to neonates and direct exposure to virus during passage through the birth canal.’ However the two studies cited in the report in support of the hypothesis do not prove it and are tentative only.

82. The organising hypothesis of the HIVNET 012 experiment was therefore merely speculative. That the hypothesis is bad is borne out by the fact that throughout their pregnancies mothers and foetuses share the same fluids. Any virus with which the mother is infected would therefore have nine months to reach and infect the child, not just a few hours of labour via the speculative vectors proposed by the HIVNET 012 researchers. In the premises, administering nevirapine at the onset of labour to prevent HIV transmission must invariably be too late.

83. The HIVNET 012 researchers failed to take account of the fact that it takes an average of 4.6 hours for an oral dose of 200 mg to reach its maximum concentration in the blood. Since women generally deliver at between 0.9 and 10.5 hours after dosing, and nevirapine takes between 1-8 hours to reach maximum plasma concentration, an unascertained number must give birth before the target concentration can be reached. Accordingly, a single dose of nevirapine administered to women going into labour will, on average, always be too late to prevent transmission for about half of them.

84. The fundamental flaws in the design and execution of the HIVNET 012 study, evident from the report of the trial itself, even without regard to the contents of the missing case files, are inconsistent with
LaMontagne’s loose statements that: ‘There is absolutely no evidence that I know of that the effectiveness of nevirapine ... has been compromised ... There is no question that the drug works. ... We believe the studies were done to extremely high standards and that they were done properly and ethically. ... I don’t think that anyone is alleging that anything was improperly done.’ On a considered analysis, the HIVNET 012 clinical drug trial was so radically flawed in its design, conduct and interpretation that no drug licensing authority acting reasonably can accord it any weight.

85. The implications for the South African public of the unverifiability of the reported data in HIVNET 012, and their worthlessness on their face in any event, are that, in terms of a wide-scale court-mandated programme, South African women and their babies are to be treated with a profoundly poisonous chemical compound having no proven clinical benefits.

86. The hearings of both the High Court application for a mandamus to enforce this programme, as well as the Constitutional Court appeal against it, proceeded from the premise that HIVNET 012 established the safety and efficacy of nevirapine.

87. The failure of the State’s legal representatives to argue the root flaws of HIVNET 012, rendering its positive conclusions for perinatal nevirapine treatment completely invalid, resulted in the High and Constitutional Courts proceeding from a foundation of agreed facts that were fallacious, and both Courts were fundamentally misdirected on the facts accordingly.

88. The perinatal administration of nevirapine to pregnant HIV-positive women and their babies in South Africa will result in an unacceptable and pointless hazard to them.

89. No effective machinery exists in South Africa, akin to MedWatch established by the FDA in the US, for monitoring the predictable harm caused by the perinatal administration of nevirapine to mothers going into labour and then their babies after birth.

90. The victims of this programme will almost exclusively be poor black women and their children, whose special vulnerability to the well established profound toxicity of nevirapine is likely to be exacerbated by their poverty-weakened health.

91. Since the benefits, if any, and the full extent of the harmfulness of nevirapine to this especially vulnerable class of people have yet to be defined, a programme of nevirapine administration to poor black women and their babies across the country amounts to an open-ended, dangerous experiment upon them.
92. In the gamble, nevirapine manufacturer BI stands to make a certain financial gain, whereas poor black South African women and their babies stand to lose their lives and their health by way of acute toxic insult or the consequent onset of life-threatening opportunistic infections, *inter alia*, that are the well-known concomitants of exposure to chemotherapeutic agents.

93. In the situation, the perinatal administration of nevirapine in South Africa is a violation of the Hippocratic Oath, and of international medical conventions concerning medical experiments on humans.

94. It is unreasonable and indefensible that a toxic drug not approved anywhere in the First World for perinatal administration, should be supplied to poor black women and their babies in South Africa on the false premise that it has been shown to be both effective and safe.

95. None of the 53 countries named by BI in a list it supplied to the MCC on 22 April 2002, in which nevirapine is licensed for perinatal administration, are modern First World industrial countries falling within the ‘north’ of the north/south development divide. In plain terms and in practical effect, nevirapine is not considered fit for perinatal administration to whites.

96. The pharmaceutical industry’s persistent promotion of dangerous drugs in the ‘south’ for indications prohibited in the ‘north’ is a well-documented, unconscionable abuse of vulnerable markets.

97. If nevirapine is not accepted by the drug licensing authorities of any First World countries as safe and effective for perinatal use, there can be no reasonable justification for the MCC applying a lower standard when assessing its safety and efficacy.

98. Nevirapine is omitted from the CDC’s latest revised recommendations for preventing perinatal HIV transmission, issued on 17 May 2002. This implies that in the view of the CDC, HIVNET 012 does not establish the efficacy and safety of nevirapine for pregnant women and their babies in America.

99. Having regard to the foregoing, a failure by the MCC to intervene by withdrawing BI’s provisional licence to supply nevirapine for perinatal administration in South Africa, alternatively, suspending it *pro tem*, will constitute an unreasonable breach of its statutory duties to the South African public to protect it from the sale of useless and harmful medicines, alternatively, medicines that have not been shown to be both effective and reasonably safe. I am advised that such dereliction would be unlawful and would consequently be subject to judicial review and compulsion.
100. I am further advised that any ‘Informed Consent’ to nevirapine treatment and its risks granted by any pregnant woman treated at a public hospital, who has not been fully informed of all the facts detailed herein, will be idle, and any harm suffered through nevirapine exposure will consequently be actionable, *i.e.* unless patients are so informed, the state will face massive exposure to civil liability for damages in a potentially limitless and uncontainable run of toxic tort actions, brought by women and children injured by perinatal nevirapine treatment, whether the injuries be fatal or slight, immediate or long-term.

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Dear Ms Matsoso

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

We record that we have received no response or even acknowledgement of our letter to Council of the 22nd ultimo in the above matter, delivered by courier to your offices at 8h54 on the 24th. In the circumstances, we thought fit to make copies available to a wide spectrum of media and interested parties, including hardcopies hand-delivered to President Mbeki and National Minister of Health Dr Tshabalala-Msimang. At the latter’s request, we have provided her with further copies of our first letter, together with sufficient copies of the instant one, for distribution to all members of Cabinet and all Provincial Health MECs.

We have taken note of the contents of Council’s press statement of 12 July concerning the use of nevirapine to prevent mother to child transmission of HIV (pMTCT), following its meeting ten days earlier. (A copy is annexed for easy reference.) Regrettably, we must agree with the criticism of Professor James McIntyre, lead researcher at the Chris Hani-Baragwanath Hospital Perinatal HIV Research Unit, that it is ‘confusing and unfortunately badly worded’. Indeed, we find it incoherent and incomprehensible.

It is evident that none of ‘the issues’ listed as having been ‘considered’ by Council during its ‘deliberations’, included any of the efficacy and safety questions raised in our letter and traversed in the papers referred to therein. Three of the four ‘issues’ that Council ‘considered’ were in fact one: the potential for drug ‘resistance’ emerging among mothers administered a single dose of nevirapine during labour – a matter that must obviously rank second to the primary issues of the efficacy and safety of the drug for babies for the prophylactic purpose intended.
The statement recalls that that ‘the approval of nevirapine’ for pMTCT ‘was conditional upon monitoring of resistance and its impact on efficacy’. In other words, in specially licensing the drug for pMTCT, Council accepted that its efficacy and safety had been established by HIVNET 012 (the ‘pivotal study’ as Council described it in its resolution of 25 July 2003) – but before granting the drug final approval in the form of unconditional registration for this special indication, Council sought assurance from Boehringer Ingelheim, in the form of further research data, that the use of the drug would not lead to the development of drug resistance.

It is evident from point ‘iv’ of the statement, in which Council records its ‘view ... that nevirapine monotherapy is less efficacious than combination regimens’, that Council’s ‘deliberations’ at its 2 July meeting proceeded from the premise that the efficacy of nevirapine given solo had been demonstrated – notwithstanding its resolution a year earlier to reject the pivotal study that had founded its special registration of nevirapine for pMTCT.

In issuing its ‘Recommendations on ARVs and MTCT prevention 2004’ (7 January 2004 draft, published online, hereinafter referred to as ‘the WHO Recommendations’), to which Council referred in point ‘iv’, the World Health Organisation also considered that the ‘efficacy [of] NVP alone in two single-dose regimens to the mother and the infant ... has been demonstrated’. As authority for this claim, the WHO cites HIVNET 012 – thrown out by the US FDA in March 2002, and by Council in July 2003. The WHO also cites the local SAINT trial – expressly dismissed by Council in its July 2003 resolution, presumably because it does not meet the basic criteria for a clinical drug trial to be considered a pivotal study. Nowhere in any other drug regulatory jurisdiction is the SAINT trial regarded as up to standard as such.

We mentioned in our first letter that nevirapine is not considered proven safe and effective for administration to American women in labour and their newborn babies, and is not included in the US CDC’s current guidelines for pMTCT. We draw your attention to the fact that nevirapine is likewise not recommended for this special indication for British mothers and babies in the United Kingdom, and the drug is not included in the current guidelines for pMTCT published by the British HIV Association (BHIVA) in October 2001. We reiterate: it is only on mothers and babies in the developing world that the US government (at the level of the State Department, no less) and officials of the WHO (under its sway) urge the drug.

Council refers in point ‘iv’ to a ‘number of recent studies’, including the WHO Recommendations, in support of its view that ‘combination
regimens’ are more ‘efficacious’ than ‘nevirapine monotherapy’. Apart from the latest combination-drug study by Lallemant et al., published in mid-July in the New England Journal of Medicine, the ‘recent studies’ purportedly supporting the use of AZT, 3TC and nevirapine in combination during pregnancy, labour and post-partum are cited in the WHO Recommendations as references 12-19.

We have reviewed these studies, as well as the latest one in the NEMJ. All of them share the following basic and fatally destructive methodological defects:

Mothers were incompetently diagnosed as HIV-infected with antibody tests (ELISA and sometimes Western Blot), manufactured and licensed for blood screening only – and not for diagnostic use – on account of their well-established non-specificity. No antibody test kit manufacturer, of either type, claims that antibody reactivity ipso facto indicates infection with HIV. On the contrary, the medical literature abundantly establishes that it doesn’t, but this is perhaps a matter falling less within Council’s province than the Medical Research Council’s – a matter that it has yet to examine.

Babies in the trials cited by the WHO, and the latest one in the NEMJ, were diagnosed as having been infected with HIV during pregnancy or birth by means of RNA-based tests utilising PCR technology – in some cases ‘qualitative’ tests, in others ‘quantitative’. But the specificity of such tests is unascertained. Accordingly, in the case of the former, Roche Diagnostic Systems, Inc. explicitly cautions: ‘For research use only. Not for use in diagnostic procedures.’ And in the case of the latter: ‘The Amplicor HIV-1 Monitor test is not intended to be used as a screening test for HIV or as a diagnostic test to confirm the presence of HIV infection.’ These express contraindications for the use of the tests as diagnostic instruments have simply been ignored by the researchers who designed and conducted the MTCT studies under discussion – on the assumption, apparently, that RNA-based test readings of the type employed yield definitive diagnostic results, comparable with highly probative DNA matching in forensic applications. In fact this is not the case: such tests are so unreasonably non-specific that they are not even permitted by their manufacturers, or the FDA, for commercial blood screening, let alone for making diagnoses in drug trials (or for any other diagnostic purpose).

It is so that in defiance of the manufacturer’s explicit contraindication, and the limited, particular non-diagnostic purpose for which the FDA has licensed RNA assays for clinical use (therapeutic treatment response monitoring only), the US CDC inexplicably permits the use of RNA assays for determining HIV infection in babies – but only in the case of
possible MTCT of HIV, and not in cases of suspected infection by blood transfusion or in other way, in which case the CDC reverts to its prohibition on the use of RNA assays to determine whether babies are infected or not. But even this irrational and indefensible exception made by CDC officials does not extend to clinically diagnosing HIV infection among babies: the CDC supports the exceptional use of RNA assays in possible MTCT cases for ‘surveillance purposes’ only, and not for making a ‘clinical diagnosis’ of HIV infection.

Notwithstanding this, on the basis of clinical drug trial findings based on these all-but-meaningless test results, babies in the developing world are to be exposed in utero and post-partem on the advice of the WHO to exceedingly toxic chemicals, on the fallacious ground asserted by Council, and the WHO, that they have been shown to demonstrate anti-HIV prophylactic activity.

None of the pMTCT studies under discussion were double-blind, placebo-controlled trials of such quality and cogency as to qualify them as pivotal studies for drug licensing purposes in any first world country – or in any developing country like ours, in which, it is clear from the US NIH’s final Remonitoring Report on its admittedly botched HIVNET 012 study, released to Council in April 2003, US health officials evidently believe lower standards for demonstrating the safety and efficacy of drugs should apply.

In the case of nevirapine in particular, therefore, we have the incredible situation in South Africa in which, having failed to make the grade as proven safe and effective when used alone perinatally, the drug has now been passed by Council for this special and especially dangerous indication provided that it is combined with another extremely toxic drug, AZT. This new treatment protocol ‘recommended’ by Council is clearly based squarely on the WHO Recommendations.

Before we address the disgraceful deficiencies of this grossly partisan, pro-pharmaceutical-cartel document from the WHO, we wish to remind Council of the quality of professional expertise emanating from that body, as illuminated by a report in the New York Times on 25 November 1999, following President Mbeki’s order that the safety of AZT be investigated. “‘To combat a fatal disease, it is perfectly acceptable to use drugs slightly more toxic than an aspirin” ... said Dr. Joseph Perriens, who heads the care and support program of the United Nations AIDS program in Geneva.’ Sigma Chemical Co. in the US takes a rather different view of the matter, evident from the labelling of AZT that it manufactures for research use. Alongside a skull and crossbones emblem, with ‘Toxic’ below it in six different languages, set against a bright orange stripe to signify deadly chemical hazard, the label on bottles containing as little as
25mg cautions: ‘TOXIC Toxic to inhalation, in contact with skin and if swallowed. Target organ(s): Blood Bone Marrow. In case of accident or if you feel unwell, seek medical advice (show the label where possible). Wear suitable protective clothing.’ (See enlarged photograph of AZT bottle annexed hereto. The bottle, in the possession of the writer, is available for inspection.)

The assumptions, methods and interpretation of the sort of MTCT drug studies cited by the WHO have been extensively critiqued by Papadopulos-Eleopulos et al. in the monograph and PowerPoint slideshow mentioned in our first letter. Even more fundamentally, GlaxoSmithKline’s basic claim that AZT acts as a chain terminator of proviral HIV DNA, and thereby works as an antiretroviral agent, was meticulously dismantled and debunked by the same core group of scientists in A Critical Analysis of the Pharmacology of AZT and its Use in AIDS, published as a special supplement to Current Medical Research and Opinion Vol. 15, 1999. In short, the drug does not achieve meaningful intracellular levels of its active form (AZT-TP) in vivo, and is therefore incapable of the therapeutic effect that its manufacturer GlaxoSmithKline claims for it. Nonetheless, AZT remains extremely toxic to all cells. The risk-benefit ratio is accordingly infinite.

With all due respect, it is inconceivable that Council’s members read and comprehended the purport of these papers before issuing their latest drug combination recommendation for pMTCT, and it raises the problem identified by President Mbeki in an interview in the Sunday Times on 6 February 2000: Criticised by Nature’s local correspondent Dr Michael Cherry for having ordered an enquiry into the safety of AZT the year before, the President responded by forwarding him a copy of Papadopulos-Eleopulos’s et al. AZT pharmacology analysis to read. Cherry replied by requesting time to consult his colleagues before answering, admitting that he knew very little about the subject. Medical Research Council president (at the time) Dr William Makgoba had also reacted ignorantly to the President’s stated concerns about the drug, saying, ‘I’ve read nothing in the medical literature indicating that AZT should not be given to people’ – shortly after the publication of the just-mentioned paper, and a host of severe toxicity reports, including gravely crippling and sometimes fatal foetal toxicity, in the preceding months. Remarking on their professional indolence and irresponsibility, President Mbeki asked, ‘What do you do if professors won’t read articles about subjects they write about? What do you do?’ Indeed.

The published literature on the extreme toxicity of AZT, particularly the compound’s toxic effects on human, primate and rodent foetuses, is substantial, but a conveniently assembled collection of excerpts from
some published papers on this subject, prepared by the writer’s associate David Crowe in Calgary, Canada, is annexed hereto. Please note that the list is not exhaustive, and there are many more. See also *Debating AZT: Mbeki and the AIDS drug controversy* by the writer, in paperback herewith and saved to the enclosed CD, and the manuscript of the writer’s new book in manuscript, also saved to disc, ‘*Just say yes, Mr President*: Mbeki and AIDS*, which canvasses the new literature on AZT toxicity published in the last two and a half years since the publication of *Debating AZT*. The new book manuscript describes the fraudulent circumstances in which the drug was licensed in the US and elsewhere in a dedicated essay in the appendices, *Licensing AZT*.

We wish to highlight that when the effects of exposing babies to AZT in utero is assessed clinically, as opposed to using surrogate markers for drug efficacy, the published research consistently – and predictably – reveals that AZT-exposed babies have a higher mortality rate, higher rate of congenital anomalies, neurological defects, immunological disorders and other serious disease than unexposed babies. It raises the question why this drug is ever given to pregnant women in the first place, other than for commercial reasons. It is difficult to credit that Council was aware of this literature in recommending the drug for administration to this class of patient.

An appalling feature of the WHO Recommendations is the manner in which the significance of the human foetal toxicity literature cited is consistently underplayed – where it is mentioned at all, with most of the corpus on this subject omitted from consideration.

The WHO Recommendations allege: ‘Although theoretically ZDV [AZT] may have mutagenic and carcinogenic effects ... no adverse effects have been reported from any trials or studies on ZDV-exposed children.’ This statement is false, contradicted by the findings of Kumar et al. and Newschaffer et al., whose studies are cited in David Crowe’s ‘AZT: A Collection of Citations from the Medical Literature’ and discussed in numbered paragraph 35 of *Debating AZT*.

Kumar et al., ‘reviewing the frequency of birth defects’ among one hundred and four babies exposed to AZT in utero in India, found eight out of eighty live births grossly malformed, including holes in the chest, abnormal indentations at the base of the spine, misplaced ears, misshapen faces, heart defects, extra digits and albinism. Eight foetuses exposed to the drug died in the womb, and a further eight had to be therapeutically aborted. In their study of 1932 live-births among AZT-treated pregnant women in New York State, Newschaffer et al. found an almost trebled rate of ‘major ... congenital anomalies’ among AZT-exposed babies.
Furthermore, a small ‘study of 195 mother-infant pairs’ by Jungmann et al. found that ‘exposure to the combination of ART and folate antagonists [e.g. GlaxoSithKline’s common antibiotic Bactrim (co-trimoxazole)] was associated with a significantly higher risk of congenital abnormalities. ... Congenital malformations were observed in nine infants (4.6%).’ The researchers accordingly wondered in *Sexually Transmitted Infections* 2001 Dec; 77(6):441-3 Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities?

Richardson et al. had suggested an affirmative answer a year earlier, reporting in *European Journal of Obstetrics, Gynecology and Reproductive Biology* (2000 Dec;93(2):215-7) two cases of severe Spinal malformations in the fetuses of HIV infected women receiving combination antiretroviral therapy and co-trimoxazole.

The WHO Recommendations claim: ‘There have been reports of a small number of serious adverse effects possibly associated with exposure to ART in the form of mitochondrial dysfunction (43-45), but an increased rate of serious clinical manifestations has not been confirmed by other studies (46-48).’

On the contrary, and in truth, Barret’s et al. findings (cited in reference 44) reported in the self-explanatory title, ‘Persistent mitochondrial dysfunction in HIV-1 exposed but uninfected infants: clinical screening in a large prospective cohort’ were indeed confirmed by the same authors in the same journal later in the year in December 2003 – but the WHO Recommendations neglect to mention this key study: ‘The finding that the use of antiretroviral nucleoside analogues in the perinatal period is associated with persistent mitochondrial disease is confirmed ... a risk about 30 times higher than that in the general population. ... Despite active screening, no similar cases were found in the antiretroviral unexposed group. ... by age 18 months ... a coherent syndrome is appearing with three main features: neurological symptoms (principally developmental retardation, seizures and behavioral disturbances), significant abnormalities on cerebral MRI (principally lesions of the white matter and brainstem) and often hyperlactataemia either persistent or transient outside the treatment period. First described as a myopathy associated with zidovudine, the issue of mitochondrial toxicity of nucleoside analogues is currently a growing problem. Its clinical expression is highly variable, from peripheral neuropathy to severe lactic acidosis.’

Blanche et al. (reference 43 in the WHO Recommendations) noted the sort of consequences of ‘persistent mitochondrial dysfunction’ caused by in utero exposure to AZT (combined in some cases with 3TC, a closely
similar drug): eight children in their study were born with severely impaired energy metabolism and corresponding muscle and other cell damage, manifesting in heart muscle injury and muscle weakness generally. Five children, of whom two died, presented with delayed neurological symptoms – extensive brain damage in the form of massive cortical necrosis, cortical blindness, epilepsy and spastic quadriplegia, and three were described as ‘symptom-free’ but had ‘severe biological or neurological abnormalities’.

In view of Council’s members’ manifest failure to have read and considered the papers to which we referred in our first letter, as well as Papadopulos-Eleopulos’s et al. seminal examination of the molecular pharmacology of AZT published in CMRO, we enclose copies for their belated perusal, after which, in acquitting themselves of their professional obligations to the South African public, particularly to unborn and neonate children most vulnerable to the toxic effects of dangerous chemicals, we trust and expect that they will (a) immediately reconvene to recall their recommendation earlier this month that pregnant women and their babies in South Africa be exposed to AZT and nevirapine, (b) issue an urgent contra-indication directive in this regard, and (c) conclude their review of the special registration of nevirapine for pMTCT by revoking it, in view of Boehringer Ingelheim’s failure to meet the terms set in Council’s resolution of 25 September 2003.

Having done this, we further expect that Council’s members will finally address their minds to the AZT triphosphorylation problem identified five years ago by Papadopulos-Eleopulos et al. in their epochal AZT biochemistry paper, and will thereafter resolve to deregister the drug before any more South Africans are pointlessly poisoned with it – as millions were crippled and killed by their doctors’ mercury and arsenic treatments less than a century ago. Whereas President Mbeki is familiar with and understands this basic (and insurmountable) biochemical problem with GlaxoSmithKline’s claims for its product (he has twice been quoted in the press referring to it), it does not appear that anyone on Council is even aware of it. We appreciate that studying Papadopulos-Eleopulos’s et al. radical re-investigation of the biochemistry of AZT will require considerable application and effort, because the paper is long and technical, but it is precisely for taking such trouble that Council’s members are paid their salaries. For maximum transparency, we suggest that in the course of its review of its registration of AZT as an allegedly antiretroviral drug, public hearings be conducted by Council at which GlaxoSmithKline’s core claims about the pharmacological activity of its drug be openly debated before it. We propose that submissions in this regard be presented orally, supported by written synopses. This will facilitate judicial review of the process should this become necessary.
Under its current leadership, South Africa has refused to conduct itself as the errand boy of the North. It is to be hoped that Council will exhibit the same independence of mind and political courage, will and innovativeness in relation to AZT – the original and still biggest-selling AIDS drug, currently turning over more than a billion dollars worth every year.

We conclude by pointing out that AZT was first synthesized in 1961 by Professor Richard Beltz (not in 1964 by Dr Jerome Horwitz as is generally reported) as an experimental cell-poison (not anti-viral agent) for possible cancer chemotherapy, under the aegis of the American cancer research programme. (The writer has a detailed history of the process, which Beltz personally recounted to him; see Inventing AZT in the appendices to ‘Just say yes, Mr President’: Mbeki and AIDS.) Reviewing an early draft of the writer’s review of the toxicity literature on the drug in Debating AZT: Mbeki and the AIDS drug controversy, Beltz remarked approvingly, ‘... you are justified in sounding a warning against the long-term therapeutic use of AZT, or its use in pregnant women, because of its demonstrated toxicity and ... devastating effects ... Your effort is a worthy one ... I hope you succeed in convincing your government not to make AZT available.’

Council, on the other hand, against the vehement advice of the inventor of AZT, considers that South African pregnant women and their babies, mostly black and poor, should be prescribed this poison to ingest as a beneficent medicine – but only when combined with another equally toxic chemical, nevirapine. The WHO Recommendations’ concession that ‘there is still a lack of information on the effects of short-courses of ARVs to prevent MTCT on the long-term health of the infected mother (and that of her infected infant) ... but research is ongoing’ didn’t cause Council any disquiet, apparently – even though South Africa is ill-equipped to monitor the extent to which mostly African children, ‘infected’ or otherwise, will be maimed or possibly killed by the experimental toxic treatment.

There are scientifically proven safe and effective alternatives to these toxins for people diagnosed HIV-positive: the latest major study by Fawzi et al. of the Harvard School of Public Health reports the direct, clinically observable health benefits that micronutrient therapy provided to a large cohort of HIV-positive patients, and it confirms more than a decade of positive research findings on micronutrient supplementation for AIDS, including many local studies. These latest findings, published at the beginning of this month in the New England Journal of Medicine, are consistent with numerous preceding studies reporting the benefits of multivitamin and other micronutrient therapies, which can be read archived at: www.dr-rath-foundation.org/nhc/researcharchive.html.
By contrast, no reputable study of the effects of antiretroviral drugs has shown comparable clinical benefits to date. That these nutritional elements are not patentable, and so do not yield the sort of profits for the pharmaceutical cartel generated by so-called antiretroviral drugs, should not be a factor detracting from Council’s consideration of these alternatives the next time it formulates its recommendations for the treatment of HIV-positive people and AIDS patients. We propose that, coordinated by Council, clinical trials involving these proven safe and effective alternative treatment approaches be conducted by the Medical Research Council immediately, and we request an audience before Council to present all the data available in this regard with a view to assisting with the design of the trial protocols. Since, for obvious reasons, it is essential that corporate influence over such a study be contained, we suggest that a senior, scientifically independent scientist/clinician of the academic stature of Professor Sam Mhlongo, Head of Department, Primary Health Care and Family Medicine, MEDUNSA, be appointed as Principal Investigator.

We hereby put Council on notice that failing a satisfactory considered response to this and our preceding letter within fourteen days of the delivery hereof, or within such extended period as may be agreed, it is our intention to institute proceedings to compel. We will simultaneously propose to Dr Tshabalala-Msimang that she reconvene the Dukes Committee, appointed by her predecessor in 1997 to inquire into the professional competence of Council’s incumbents at the time, so that the dead wood on Council again be given the sack.

Yours faithfully

ADV ANTHONY BRINK
CONVENOR AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP

Cc: The South African government, and other interested parties.
MCC MEDIA RELEASE: 12 July 2004

MCC NO LONGER RECOMMENDS THE USE OF MONOTHERAPY IN PREVENTING MOTHER TO CHILD TRANSMISSION OF HIV

The South African Medicines Control Council (MCC) reconsidered the merits of nevirapine when used as a monotherapy to reduce the risk of transmission of HIV from mother to child during labour. Council believes that the risk-benefit profile of nevirapine monotherapy has changed and therefore no longer recommends its use for the prevention of mother to child transmission (PMTCT) of HIV.

At a recent meeting of the MCC held on 2 July 2004, Council recommended that nevirapine and zidovudine (AZT), previously approved for monotherapy in PMTCT, only be used in combination therapy.

The approval of nevirapine as monotherapy for this indication, in April 2001, was conditional upon monitoring of resistance and its impact on efficacy.

In its deliberations, the MCC considered the following issues:

(i) Nevirapine leads to significant resistance in mothers and babies when used as a monotherapy to reduce the risk of transmission of HIV from mother to child compared to a combination therapy;

(ii) Recent studies conducted in South Africa, using nevirapine as a monotherapy for this purpose, show significant resistance of up to 50%;

(iii) The clinical significance of these findings needs further investigation as the efficacy of future treatment options in mothers or babies who have nevirapine-resistant HIV may be compromised;

(iv) A number of recent studies, including an expert consultation report of the World Health Organisation (February 2004), confirms the view of the MCC that nevirapine monotherapy is less efficacious than combination regimens;

(v) Council’s decision applies to all monotherapy interventions when used to reduce the risk of transmission of HIV from mother to child during labour. Council is of the view that combination therapy should be considered for this indication.

The Department of Health has introduced a Comprehensive Plan for Management, Care and Treatment of HIV and AIDS; which introduce ARV’s and the opportunity of combination therapy.
Annexure ‘B’
AZT: A Selection of Citations from the Medical Literature
collated by: David.Crowe@aras.ab.ca

The citations are grouped under the following categories:
- Harmful Effects on Blood and Bone Marrow
- Harmful Side Effects, General
- Muscle Disorders (including Heart)
- Warnings from Experiments with Animals
- Increased Risk of Sickness and Death with AZT
- Lack of Effectiveness ... and Toxicity
- AZT and Mitochondria
- AZT and Pregnant Women and Children

Harmful Effects on Blood and Bone Marrow

AZT is known to suppress the ability of the body to produce red blood cells (anemia) and white blood cells (*-penia, e.g. neutropenia -- deficiency of neutrophils or pancytopenia -- deficiency of all types of cells).

Zidovudine was generally well tolerated in this high-risk population ... [from Table II: 32%-Anemia grade >=2; 11%-Neutropenia; 13%-Thrombocytopenia; 45%-Received transfusion; 26%-Received erythropoetin; 11%-HIV infection; 8%-Died] ... Slightly more than half of the subjects had anemia severe enough to require a transfusion [giving new meaning to the term ‘well tolerated’]


Recent epidemiologic studies of HIV-related anemia have strongly and repeatedly associated low hemoglobin level with disease progression and mortality. Patients who are at greater risk for anemia may include those of African-American ancestry, and those with low CD4 cell counts, high virus load, and low mean corpuscular volume and those receiving zidovudine [AZT] ... [in one study] for patients without anemia, 3.1% died by 12 months. In contrast, for patients with mild anemia, 15.9% had
died, and for patients with severe anemia, 40.8% had died [this association remained even after controlling for CD4/viral load measurements]


We conducted a longitudinal study of 797 human immunodeficiency virus (HIV) positive women (7732 visits) and 389 HIV-negative women (3651 visits) to characterize anemia ... Risk factors for anemia [included] zidovudine use [1.14 times more likely]. Anemia was common and associated with an increased risk of death (hazards ratio, 1.64; 95% CI, 1.21 2.23) among HIV-positive women ... the mortality rate during the follow-up period was 37% in those who were anemic at enrollment and 22% in those who were not anemic at enrolment


1 patient [out of a grand total of 10 in this clinical trial] suffered from severe anemia resulting from ZDV [AZT] therapy.


In a retrospective evaluation of medical records of 32,867 HIV-infected persons followed in nine cities in the United States, the 1-year incidence of anemia, defined as a hemoglobin level <10 g/dl or a physician’s diagnosis of anemia, was approximately 37% for patients with a clinical AIDS-defining condition; 12% for those with immunologic AIDS, defined as a CD4 count <200; and 3% for persons without either of these conditions ... Use of ZDV either currently or in the past 6 months was associated with anemia ... A total of 41.5% of those with a history of ZDV in the past 6 months and 27.7% of those without such history were anemic at baseline ... The strong statistical associations between worsening parameters of HIV disease and increased likelihood of anemia ... suggest that effective antiretroviral therapy may be associated with improvement in Hb [hemoglobin] levels [!]

Of variables related to HIV infection, low CD4+ cell count, AIDS diagnosis and receiving zidovudine [AZT] therapy were predictive for prevalent anemia


We found that 78.2% of the patients with mild or severe anaemia at baseline had received zidovudine [AZT]


While effective drug therapy is continued in zidovudine[AZT]-treated HIV-infected patients ... PROCRIT Reduces Transfusion Requirements and Helps Lift the Burden of Anemia.

Advertisement for PROCRIT. 1997

178 subjects (34%) had a hemoglobin concentration below 5 mmol per liter [anemia] ... A greater proportion of subjects in the standard-treatment [high dose AZT] group had a first episode of severe anemia earlier in the study, as compared with the proportion in the low-dose group. 134 subjects (26%) received red-cell transfusions (65 in the standard-treatment group and 69 in the low-dose group) ... 230 subjects(44%) had a [low] neutrophil [infection fighting white blood cells] count ... 134 (51%) in the standard-treatment group and 96 (37%) in the low-dose group ... 22 subjects (4%) had a [low] platelet [blood clotting cells] count.


Zidovudine is well known to produce haematological toxicity in vitro and in some patients ... It is worrying that bone marrow changes in patients on zidovudine seem not to be readily reversed when the drug is withdrawn ... These findings have serious implications for the use of zidovudine in HIV positive but symptom-free individuals.
Between 10% and 25% of patients experienced decreases in granulocyte counts to less than 750/cubic-mm during each month of therapy ... The incidence of anemia remained relatively constant over time. Approximately 10% of patients per month reported with hemoglobin levels less than 7.5 g/dl, and fewer than 5% were reported with levels less than 6.5 g/dl ... At the physicians’ discretion, transfusions with packed red blood cells were used to manage hemoglobin levels in patients with anemia [Figure 4 shows that 20-25% of patients required transfusions during the main portion of the trial (12-52 weeks)] ... Anemia and granulocytopenia remained the major reasons for dose reductions or discontinuation of zidovudine treatment.


nearly one half of patients treated with AZT for [HIV]-associated disease develop transfusion-dependent anaemia due to bone marrow depression


Blood transfusion is often necessary in patients with AIDS, especially in those receiving AZT, a drug which produces severe anaemia in a proportion of recipients. Forty nine (36%) of 138 patients treated with AZT ... required blood transfusion at least once.


In the current study, transfusion-dependent anemia occurred in 6 of 15 patients with AIDS and Kaposi sarcoma who were receiving zidovudine therapy. All 6 affected patients required their first blood transfusion between 3 and 9 weeks after starting zidovudine therapy, and each required 4 to 14 units of packed erythrocytes to maintain a hemoglobin level above 100 g/L over a 12-week study.

The hematocrit [red blood cell count] decreased in the same patients ... with three of eight patients requiring red-cell transfusion by the fourth week of treatment.


Four patients with [AIDS], and a history of Pneumocystis carinii pneumonia developed severe pancytopenia [marked decrease in all types of blood cells] ... 12 to 17 weeks after the initiation of azidothymidine (AZT) therapy ... Partial bone marrow recovery was documented within 4 to 5 weeks in three patients, but no marrow recovery has yet occurred in one patient during the more than 6 months since AZT treatment was discontinued.


Anemia ... developed in 24% of AZT recipients and 4% of placebo recipients (P<0.001). 21% of AZT recipients and 4% of placebo recipients required multiple red-cell transfusions (P<0.001). Neutropenia (<500 cells per cubic millimeter) occurred in 16% of AZT recipients, as compared with 2% of placebo recipients (P<0.001).


more than half of all AIDS patients may not benefit from the drug because it is more toxic for them than their AIDS infection. The most serious side effect of AZT is to suppress the bone marrow, leaving patients highly vulnerable to bacterial infections


Harmful Side Effects, General

*AZT has a wide range of side effects. Those that have not been reported widely enough to deserve their own section are reported here.*
Perinatal treatment with 3’-azido-3’-deoxythymidine (AZT) has been found to reduce the rate of maternal-infant transmission of HIV; however, AZT is clastogenic at therapeutic doses in adult patients and induces cancers in the offspring of mice treated in utero. The purpose of the present study was to investigate the mutagenicity of AZT at the hypoxanthine-guanine phosphoribosyltransferase (hprt) locus of the human lymphoblastoid cell line, TK6, following in vitro exposures. ... There was a significant increase over background in hprt Mfs [mutation frequencies] in TK6 cells exposed to 300mM AZT for 3 days (1.8-fold increase). In cells exposed for 6 days, there was a decrease in ... cell survival. ... These preliminary results indicate that AZT treatment is mutagenic and produces large deletions in human cells.


AZT ... induces significant toxic effects in humans exposed to therapeutic doses ... Cytogenetic observations on H9-AZT cells showed an increase in chromosomal aberrations and nuclear fragmentation when compared with unexposed H9 cells ... The toxicities explored here suggest that the mechanisms of AZT induced cytotoxicity in bone marrow of the patients chronically exposed to the drug in vivo may involve both chromosomal and mitochondrial DNA damage.


Clinical manifestations of ANA [Antiviral Nucleoside Analogs, such as AZT] toxicity: It is self-evident that ANAs, like all drugs, have side-effects. However, the prevalent and at times serious ANA mitochondrial toxic side-effects are particularly broad ranging with respect to their tissue target and mechanisms of toxicity: ... Haematalogical toxicity [anemia, and other blood disorders] ... Myopathy [muscle disorders] ... Cardiotoxicity [heart disorders] ... Hepatic toxicity [liver disorders] ... Peripheral neuropathy [nerve damage]

During the maintenance phase after completion of the study, 2 additional patients showed signs of severe hematologic toxicity, and one patient had severe myopathy. These toxicities were attributed to ZDV [AZT] ... Patients with previous ZDV exposure had a higher incidence of advanced HIV disease and tended to have lower, but not [statistically] significant, pretreatment CD4 lymphocyte counts


among the subjects with CD4+ [immune system] cell counts < 200/mm3, the risk of developing HIV dementia among those reporting any antiretroviral use (AZT, ddI, ddC, or d4T) was 97% higher than among those not using this antiretroviral therapy ... In addition, the findings of our analysis seem to confirm previous observation of a neurotoxic effect of antiretroviral agents. Numerous studies have linked the use of ddI, ddC, and d4T [nucleoside analogs] to the development of toxic sensory neuropathies, usually in a dose-dependent manner


[this study included US health care workers exposed] to blood from a patient with documented HIV infection [81% had AIDS] as a result of percutaneous injury (for example, a needlestick or a cut from a sharp object), contamination of mucous membranes, or contamination of nonintact skin ... From October 1988 to Jun 1992, the period when use of zidovudine [AZT] was studied, 848 workers were enrolled. Postexposure zidovudine was used by 265 (31%) of these workers ... in doses range from 200 to 1800 mg/day and for periods of 1 to 180 days ... The proportion of enrolled workers using zidovudine increased from 5% in the fourth quarter of 1988 to 50% in the third quarter of 1990 and has been stable subsequently ... no seroconversions occurred among 301 workers not using zidovudine, and 1 seroconversion occurred among 143 workers using zidovudine ... 176 (75%) reported one or more symptoms, most commonly nausea, malaise or fatigue, or headache. Symptoms were reported less frequently among workers who did not use zidovudine ... Of 175 workers who completed 21 or more days of [AZT] prophylaxis, 51 (29%) had paired hemograms at least 21 days apart ... 7 (14%) had a 10% or greater reduction in hemoglobin or hematocrit values ... 74 (31%) of
workers did not complete their planned regimen of zidovudine because of adverse symptoms (73) or reduction in hemoglobin level (1). 28 (12%) of workers were absent from work for periods ranging from 1 to 49 days because of adverse events attributed to zidovudine. Because of uncertainty about efficacy and safety, the Public Health Service concluded in January 1990 that a recommendation for or against the use of postexposure zidovudine could not be made.


16 of 38 patients developed nail discoloration after zidovudine therapy was begun. Dyschromia was usually apparent within 4 to 8 weeks but also occurred as late as 1 year.


Zidovudine was reasonably well tolerated in this study. 27% [remained] on full dose at the end of the first year of therapy. The full daily (1.2 g) was received by 68 patients (24%) for the entire duration of their time on therapy. Of these full-dose patients, six died within 6 weeks of commencing therapy. 172 patients (56%) developed a new AIDS-defining condition during therapy; 130 patients [42%] developed the condition more than 6 weeks after commencing zidovudine therapy. Anemia was the most frequently reported adverse experience during zidovudine therapy. Transfusions were reported necessary for 155 patients (50%) while on zidovudine, 91 patients (representing 29% of the total) required transfusions on more than one occasion.

Swanson CE, Cooper DA. Factors influencing outcome of treatment with zidovudine of patients with AIDS in Australia. *AIDS.* 1990;4(8):749-57

Of the 524 subjects enrolled [in this study of people in the early stages of AIDS and HIV antibodies], 4 never received zidovudine [AZT], 41 completed the study, and 479 were withdrawn from zidovudine treatment [i.e. virtually everyone]. The reasons for withdrawal from zidovudine were the development of an opportunistic infection or a neoplasm [cancer] (54 subjects); death (43); toxic reactions (183); withdrawal by the subject (169) and other reasons (30). [of the] 183 subjects
withdrawn ... because of toxic reactions, zidovudine was discontinued earlier in more subjects in the standard-treatment group than in the low-dose group [40% vs. 29%]. Among the symptoms only headache was noted more frequently in the low-dose group ... 22 subjects (8%) in the standard-treatment group and 27 (10%) in the low-dose group had elevated levels of hepatic [liver] enzyme ... 178 subjects (34%) had a hemoglobin concentration below 5 mmol per liter [anemia] ... 134 subjects (26%) received red-cell transfusions (65 in the standard-treatment group and 69 in the low-dose group) ... 230 subjects (44%) had a [low] neutrophil [infection fighting white blood cells] count ... 134 (51%) in the standard-treatment group and 96 (37%) in the low-dose group ... 22 subjects (4%) had a [low] platelet [blood clotting cells] count.


AZT inhibition of DNA synthesis in 3 hr bone marrow cultures is relatively consistent in a variety of hematologic disorders. As approximately two-thirds of AIDS patients appear to be [deficient in] folate and/or vitamin B12, the fact that AZT-induced inhibition of pyrimidine incorporation into DNA [required for DNA elongation] is occurring in cells which may be megaloblastic, i.e., in a state of impaired DNA synthesis, suggests that these cells may be more susceptible to AZT toxicity. The data also support the notion that AZT inhibition results predominantly from termination of DNA chain elongation.


58% of all subjects with AIDS and AIDS-related complex receiving zidovudine experienced granulocytopenia of grade 3 or higher ... Serious anemia occurred in 32% of all subjects receiving zidovudine ... and could be typically managed by dose attenuation, temporary dose interruption of zidovudine therapy and/or red blood cell transfusions ... 12% of subjects ... had an episode of thrombocytopenia [low platelet count] after the initiation of zidovudine therapy ... Ten patients had liver enzyme levels elevated ... and were managed with dose attenuations or interruptions of zidovudine therapy ... One report of a grand mal seizure, two events associated with cardiac dysfunction, and five reports of myopathy were the only new serious potentially drug-related adverse events reported during extended periods of zidovudine administration.
We report a patient who experienced acute cholestatic hepatitis on initial exposure to and rechallenge with zidovudine and, as a result, was unable to receive further therapy with the drug. Seven days after starting AZT therapy, the patient presented with a 2-day history of intermittent fevers and abdominal discomfort. Seven days after re-starting AZT therapy, once the initial symptoms resolved, the patient again experienced fever, right upper quadrant pain, nausea, and headache. One month later, after discontinuing AZT, the liver function tests had almost completely returned to normal and remained without significant abnormalities.


AZT was started at full dose in 260 patients, 64 with ARC and 196 with AIDS. In 58 of these patients, AZT had to be stopped at least once for a minimum of 7 days. In 142 other patients, dosage was reduced by half because of leucopenia (79), leucopenia and anaemia (32), anaemia (20), rash (3), vomiting (3), headaches and insomnia (2), myalgia (2), or hepatitis (1). 3 patients reduced the dose with no medical reason. Later on, progression of toxicity led to suspension of AZT (for at least 7 days) in 85 of the 142 patients whose treatment had been reduced to half dose. Thus AZT was stopped at least once in 143 (55%) patients who began the full-dose regimen. Because of their initial haematological status, 105 (28.8%) patients were treated from the start with half-dose AZT - toxicity led to cessation of treatment in 71 (67.6%) cases.


In a cytogenetics study performed in cultured human lymphocytes, dose-related structural (but not numerical) chromosomal alterations were noted at concentrations of 3 micrograms/ml and higher.


**Muscle Disorders (including Heart)**

*AZT causes muscle damage, which often shows up as muscle wasting or pain. It is believed that this is largely through damage to mitochondria,*
the energy regulating organelles in every animal cell. AZT may interfere with the replication of mitochondria (which have their own DNA) or with their supply of phosphates, the energy currency of cells.

Antiretroviral treatment with AZT amplified cardiac dysfunction and worsened ultrastructural features of AIDS CM [cardiomyopathy - damage to heart muscle] in TG [transgenic mice, including some genetic material believed to be from HIV] ... AZT damaged cardiac mitochondria in WT [wild-type mice (not genetically engineered)], with destruction, swelling, cristae dissolution, and fragmentation. Similarly, hearts from AZT-treated TG showed increased mitochondrial damage, but with greater intensity


Although the association of AZT with decreased cardiac contractility [cardiomyopathy=heart muscle damage] has been debated, our data indicates a strong correlation between treatment with AZT and the development of a decrease in left ventricular performance in children with HIV infection. The fact that 17 of the 19 patients in the study in whom cardiomyopathy developed had received AZT suggests that the observed decreases in left ventricular performance could have had clinical consequences ... AZT withdrawal should be considered in any child in whom cardiomyopathy develops


Long term therapy with [AZT] can induce a toxic myopathy associated with mitochondrial changes


typical mitochondrial myopathy has been reported to be expressed among many patients with AIDS treated with long-term azidothymidine (AZT) therapy ... for AIDS patients, it is urgently necessary to develop a remedy substituting this toxic substance, AZT

Hayakawa M et al. Massive conversion of guanosine to 8-hydroxy-guanosine in mouse liver mitochondrial DNA by administration of azidothymidine. Biochem Biophys Res Commun. 1991;176:87-93
A clinically significant myopathy that precedes the development of zidovudine associated mitochondrial myopathy has been a rarity in our experience.


Before 1986, when zidovudine (formerly called azidothymidine [AZT]) was introduced... the number of patients with HIV-associated myopathy was small, and myopathy [muscle disorders] was considered a rare complication of HIV infection. During the past two years [1988-1989], an increasing number of patients receiving long-term zidovudine therapy have had myopathic symptoms such as myalgia (in up to 8% of patients), elevated serum creatine kinase levels (in up to 15%), and muscle weakness. These symptoms generally improve when zidovudine is discontinued... We conclude that long-term therapy with Zidovudine can cause a toxic mitochondrial myopathy, which is indistinguishable from the myopathy associated with primary HIV infection.


In our review of our clinic patients who have received zidovudine therapy for more than 6 months, 16% (14 of 86 patients) have had persistently elevated creatine kinase values. Six percent of these patients (5 of 86) developed symptomatic myalgia and objective proximal muscle weakness. These 5 symptomatic patients had received zidovudine for an average of 45 weeks and had had creatine kinase elevations for several weeks before onset of symptoms. Of these 5 patients, 4 had creatine kinase values return to normal and symptoms resolve after zidovudine was withdrawn... Three patients were rechallenged with zidovudine: each had recurrent creatine kinase elevations at a dose of 600 mg/d. The zidovudine dose was increased to 1200 mg/d in 2 patients: after a few days, both developed recurrent muscle symptoms that again responded to dose reduction... Results of quadriceps muscle biopsies done on our patients who responded to zidovudine withdrawal showed severe myopathic changes without evidence of inflammatory infiltrates. Electron microscopy revealed many ultrastructural changes, including destruction of the sarcomere profile with z-band change in the form of streaming and rod bodies. Muscle mitochondria showed wide variation in size, swelling, degeneration and laminar bodies. ... There have been 40 case reports [to 1990] of patients who have developed myopathy while taking zidovudine...
A severe proximal myopathy, predominantly affecting the legs, seems to be a significant complication of long-term zidovudine therapy, even at reduced doses; it affected 18% of our patients who had received treatment for more than 200 days. Other drugs could not be implicated. The pathogenesis is obscure; the myopathy resolves on cessation of zidovudine, but not on dose-reduction, though there is then a risk of rebound encephalitis.


A 24-year-old woman presented in January, 1988, with a 2-week history of progressive leg weakness and difficulty in walking. She had been found to be HIV antibody positive in April 1986, and in October, 1986, Pneumocystis carinii pneumonia developed. After the pneumonia she had been on zidovudine 200 mg 4-hourly and had required three blood transfusion for consequent myelosuppression [white blood cell deficiency]. On examination there was proximal weakness but no wasting of the upper and lower limbs, tenderness of the shoulders and thighs, and preserved deep tendon reflexes. Her gait was waddling and she was unable to rise out of a chair without using her arms ... 7 days after zidovudine withdrawal, her proximal weakness and muscle tenderness had improved significantly, and muscle force was clinically normal at follow-up 2 months later.


All [four] patients had an insidious onset of myalgias, muscle tenderness, weakness, and severe muscle atrophy favouring the proximal muscle groups. Physical examinations revealed varying degrees of muscle weakness and grossly apparent atrophy. Weight loss due to muscle loss was uniformly noted; in one patient, the loss was a striking 18 kg ... Zidovudine was discontinued in three patients, who subsequently had symptomatic improvement ... The patient who continued to receive the drug had persistent [symptoms]
Warnings from Experiments with Animals

Experiments have been performed on animals that would be unethical in humans (whether they are really ethical on animals is another question). The information that they have produced about AZT is very worrying. It is generally ignored by AIDS doctors and researchers.

Antiretroviral nucleoside analogue drugs are a major constituent of highly active antiretroviral therapy (HAART), the most advanced form of treatment for HIV-1 infection. Currently, HAART combinations that include zidovudine (ZDV [AZT]) and lamivudine (3TC) are highly effective in preventing HIV-1 vertical transmission; most children are born with no evident adverse clinical effects. However, ZDV is a moderately strong transplacental carcinogen in mice, and potential long-term consequences of fetal exposure to most HAART combinations remain unknown. To model human transplacental ZDV and 3TC exposures, experiments were performed in Erythrocebus patas monkeys given human-equivalent drug exposure protocols. Pregnant monkeys were dosed with either no drug (n = 2), 40.0 mg ZDV/d (about 6 mg/kg body weight/d) for the last 50% (10 weeks) of gestation (n = 3), or with the same regimen of ZDV plus 24.0 mg 3TC/d (about 3.6 mg/kg body weight/d) for the last 20% (4 weeks) of gestation (n = 3). Multiple fetal organs were examined at term for DNA incorporation of ZDV and 3TC using two separate radioimmunoassays (RIAs). Values for ZDV-DNA incorporation were similar in fetuses exposed to ZDV alone and those exposed to ZDV plus 3TC. Values for 3TC-DNA in fetal organs were greater than or equal to values for ZDV-DNA, indicating that the total DNA damage sustained by fetuses exposed to both drugs was at least double that observed in fetuses exposed to ZDV alone. Telomere shortening, determined by Southern blot with a telomeric probe, was observed in most organs of the three animals exposed in utero to ZDV plus 3TC. No telomere shortening was evident in the unexposed fetuses, and occasional telomere shortening was found in fetuses exposed to ZDV alone. Overall, these studies demonstrate that monkey fetuses exposed in utero to the combination ZDV plus 3TC sustain a higher level of drug-DNA incorporation and show evidence of more telomere damage than monkey fetuses exposed to ZDV alone.
3’-azido-3’-deoxythymidine (AZT) is given to pregnant women positive for the human immunodeficiency virus type 1 (HIV-1) to reduce maternal-fetal viral transmission. To explore fetal mitochondrial consequences of this exposure, pregnant Erythrocebus patas monkeys were given daily doses of 1.5 mg (21% of the human daily dose) and 6.0 mg (86% of the human daily dose) of AZT/kg body weight (bw), for the second half of gestation. At term, electron microscopy of fetal cardiac and skeletal muscle showed abnormal and disrupted sarcomeres with myofibrillar loss. Some abnormally shaped mitochondria with disrupted cristae were observed in skeletal muscle myocytes. Oxidative phosphorylation (OXPHOS) enzyme assays showed dose-dependent alterations. At the human-equivalent dose of AZT (6 mg of AZT/kg bw), there was an approximately 85% decrease in the specific activity of NADH dehydrogenase (complex I) and three- to six-fold increases in specific activities of succinate dehydrogenase (complex II) and cytochrome-c oxidase (complex IV). Furthermore, a dose-dependent depletion of mitochondrial DNA levels was observed in both tissues. The data demonstrate that transplacental AZT exposure causes cardiac and skeletal muscle mitochondrial myopathy in the patas monkey fetus.

Gerschenson M et al. Fetal mitochondrial heart and skeletal muscle damage in Erythrocebus patas monkeys exposed in utero to 3’-azido-3’-deoxythymidine. AIDS Res Hum Retro. 2000 May 1;16(7):645-44

CD-1 mice exposed prenatally to 12.5 and 25.0 mg of AZT ... had statistically significant increases in numbers of liver, lung and female reproductive tract tumors. These observations have been extended to offspring at 2 years of age ... there was a 2- to 3-fold increase in the incidence (from 20% in controls to 55-60% in AZT groups) and multiplicities of lung tumors in AZT-exposed mice. The incidence of hepatocellular adenomas in the female mice exposed to prenatal AZT increase from 0 in the control group to 20% in the high dose AZT group, and hepatocellular carcinomas metastasizing to lungs were observed only in AZT-treated mice. Prenatal administration of AZT also increased the incidence of neoplasms of reproductive tract, female mammary gland epithelium and squamous cell epithelium of forestomach. AZT ... significantly reduced the incidence of hematopoietic tumors.
Diwan BA et al. **Transplacental carcinogenicity of 3'-azido-3'-deoxythimidine (AZT) in mice.** *Proc Am Assoc Cancer Res.* 1998;39:21

The AZT animals [Macaques given AZT during pregnancy] developed an asymptomatic macrocytic anemia, but hematologic parameters returned to normal when AZT was discontinued. Total leukocyte count decreased during pregnancy and was further affected by AZT administration. AZT-exposed infants were mildly anemic at birth. AZT caused deficits in growth, rooting and snouting reflexes, and the ability to fixate and follow near stimuli visually.

Ha JC et al. **Fetal, infant, and maternal toxicity of zidovudine (azidothymidine) administered throughout pregnancy in Macaca nemestrina.** *J Acquir Immune Defic Syndr.* 1998 May 1;18(1):27-38

At 1 year of age, the offspring of AZT-treated mice exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver and female reproductive organs. AZT incorporation into nuclear and mitochondrial DNA was detected in multiple organs of transplacentally exposed mice and monkeys ... AZT is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age.

Olivero OA et al. **Transplacental effects of 3'-Azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys.** *J Natl Cancer Inst.* 1997 Nov 5;89(21):1602-8

At 1 year of age, the offspring of AZT-treated mice exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver, and female reproductive organs. AZT incorporation into nuclear and mitochondrial DNA was detected in multiple organs of transplacentally exposed mice and monkeys. Shorter chromosomal telomeres were detected in liver and brain tissues from most AZT-exposed newborn mice but not in tissues from fetal monkeys. Conclusions: AZT is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age.

in adult mice, lifetime AZT administration induces vaginal tumors at a 10-20% incidence ... In newborn monkeys and mice, AZT was incorporated into DNA of many fetal tissues ... AZT appears to be a moderately-strong transplacental carcinogen [i.e. it crosses the placenta and may cause cancer in the fetus]


Hemoglobin dropped significantly in the AZT-treated animals [Macaques] after treatment began and remained low until the end of the study ... Postnatal weight increase was significantly lower in AZT-exposed infants ... Infant hematocrits taken at time of birth were lower in the AZT-exposed group ... AZT-exposed infants took three times as many sessions as controls to meet criterion on Black-White Learning, a simple discrimination task ... It took significantly more matings to achieve the six AZT pregnancies than the six control pregnancies


we have found positive correlations between the dose of AZT administered to female CD-1 mice, the incorporation of AZT into vaginal DNA, the hyperproliferation of the vaginal epithelial basal layer, and the aberrant expression of alpha-6 integrin toward the epithelial suprabasal strata of the vagina, a target organ for carcinogenesis in mice. These results suggest that there is an ordered progression of abnormal events leading to tumorigenesis in vaginal epithelial tissues.

Olivero OA et al. Vaginal epithelial DNA damage and expression of preneoplastic markers in mice during chronic dosing with tumorigenic levels of 3’-azido-2’,3’-dideoxythymidine (AZT). Cancer Res. 1994;54:6235-42

It previously has been demonstrated that zidovudine (AZT) is lethal to early murine [mouse] embryos. The effect of the drug on pre- and postimplantation embryos was examined to delineate the timing of this toxicity and to investigate its possible mechanisms. Embryos exposed in the whole mouse during preblastocyst development were unable to proceed beyond the blastocyst stage [i.e. failed to implant in the uterine wall]. Similarly, when two-cell embryos harvested from unexposed
females were exposed to low-concentration (1 microMole) AZT in vitro over 24 h, development beyond the blastocyst stage was inhibited. In contrast, drug exposure during in vitro blastocyst and postblastocyst development resulted in little or no morphologic toxicity. Further investigation revealed that preblastocyst AZT exposure resulted in the development of blastocysts with significantly lower cell numbers than control embryos. While embryonic exposure to AZT at the blastocyst and postblastocyst stages also resulted in retarded cell division, the effects were milder than those recorded after preblastocyst exposure. These data demonstrate that the critical period of AZT toxicity toward murine embryos is between ovulation and implantation and indicate that AZT directly suppresses cell division in the preimplantation embryo.


Mice receiving AZT during gestation yielded fewer fetuses ... and greater numbers of resorptions ... Exposure to AZT was highly correlated with failure to develop to the blastocyst stage ... These data indicate that AZT has a direct toxic effect on the developing mouse embryo.


The most consistent hematologic effect from treatment with AZT [in mice] was a poorly regenerative, macrocytic anemia


[in mice] AZT had a profound effect on the number of erythrocytes [mature red blood cells] and a small effect on the number of leukocytes [white blood cells] ... anemia was seen in all the mice tested at 1,000 mg/kg per day


Male and female cynomolgus monkeys were given zidovudine [AZT], 35 to 300 mg/kg per day orally, in studies of 3 and 6 months’ duration ... the
only treatment-related alteration noted was a reversible, mild to moderate, dose-related, macrocytic anemia ... In the 6-month study, bone marrow cytology ... revealed a retardation in the maturation of all cell lines, with the erythroid elements [red blood cells] being affected to the greatest degree ... Dams [pregnant female rabbits] given 500 mg/kg per day gained less weight during the dosing period, developed anemia, and showed an increased incidence of late fetal resorptions. No evidence of teratogenicity [birth defects] was seen, even though it was shown that zidovudine crossed the placenta ... Zidovudine was also studied for its ability to morphologically transform cultured BALB/c-3T3 mouse cells and was found to be positive at concentrations of 0.5 micrograms/ml and higher ... From the Department of Toxicology and Experimental Pathology. Burroughs Wellcom Co. [the manufacturer of AZT]


**Increased Risk of Sickness and Death with AZT**

*AZT, the ‘life saving’ drug, may actually accelerate illness and death.*

participants of open-label ZDV [AZT] still had four to five times the incidence of ARC/AIDS/death of participants on blinded therapy [of which approximately half were on AZT and half on placebo] ... The unadjusted hazard of ARC/AIDS/death was 4.6 times higher for participants [in the deferred group] who had received ZDV ... after adjustment for latest CD4 this became 1.6 ... There was a suggestion of a benefit in terms of [slower] progression to ARC, AIDS or death [with AZT], no effect on progression to AIDS or death, and a suggestion of an increase in mortality.

White IR et al. Impact of treatment changes on the interpretation of the Concorde trial. AIDS. 1997;11:999-1006

Extended follow-up of patients in one [AZT] trial, the Concorde study, has shown a significantly increased risk of death among the patients treated early ... where is the evidence that for a patient with a CD4 count of 450 cells per cubic millimeter and a low plasma viral level, it would not be better to wait before initiating therapy? ... In 1990 ... a patient with a CD4 count of 450 cells per cubic millimeter would have been advised to start monotherapy with zidovudine. We now tell such a patient that, in fact, follow-up data for up to 4.5 years since that time have shown no survival benefit
The mortality rate was significantly higher among [a group of 1372] patients who had received antiretroviral therapy [principally AZT] before enrollment in the clinic


None of the LTAs [long term asymptomatics] received any antiviral drugs during the study; however, 3 [of 6] rapid progressors ... were treated with zidovudine ... [and] a rapid progressor was treated with didanosine during the study.


despite the evidence that purified [blood clotting] factor VIII is beneficial in maintaining or even increasing T-cell counts, several studies testing purified factor VIII [as opposed to the older forms of Factor VIII which were 99% to 99.9% impurities] are ambiguous about its effectiveness in preventing or treating AIDS. Some of these studies have only tested partially purified, i.e. 2-10 units/mg, instead of highly purified, i.e. 2000-3000 units/mg, factor VIII. But each of the studies that are ambiguous about the benefits have also treated their patients with toxic antiviral DNA chain terminators like AZT. Indeed the study by de Biasi et al. was the only one that has tested purified factor VIII in the absence of AZT. The study by Seremetis et al. initially called for no AZT, but later allowed it anyway. Thus in all but one study, the potential benefits of highly purified factor VIII have been obscured by the toxicity of AZT.

Duesberg PH. Foreign-protein-mediated immunodeficiency in hemophiliacs with and without HIV. *Genetica.* 1995;95:51-70

Adjusted for baseline CD4 [immune cell counts] and age [correlated with lifetime exposure to clotting factor infusions], subjects [hemophiliacs] who had started on zidovudine [AZT] had increased risks, especially for AIDS [4.46 times greater risk!] and death [2.37 times]

Only 38% of the HLP [Healthy long-term positives] had ever used zidovudine [AZT] or other nucleoside analogues, compared with 94% of the progressors.


A total of 172 (96 Imm, 76 Def) participants died [169 who had taken some AZT, 3 who had only taken placebo] ... The results of Concorde do not encourage the early use of zidovudine in symptom-free HIV-infected adults. They also call into question the uncritical use of CD4 cell counts as a surrogate endpoint for assessment of benefit from long-term antiretroviral therapy ... Representatives of the Wellcome Foundation [Glaxo Wellcome manufactures AZT] who were also members of the Coordinating Committee have declined to endorse this report.


Leukopenia [white blood cell deficiency] occurred in 82% of the patients receiving early therapy and 77% of those receiving late therapy [AZT only when AIDS occurred]; 20% and 16%, respectively, had anemia. 14% and 10%, respectively, had severe leukopenia ... and 5% and 2% had severe anemia requiring transfusion. Nausea (or vomiting) and diarrhea occurred more frequently in the early-therapy group than in the late-therapy group (40% vs. 23%, respectively; P <0.01) ... The dosage of blinded study medication was reduced because of adverse reactions in 64 [38%] of the patients assigned to zidovudine (early therapy) and in 29 [17%] of those assigned to placebo (late therapy) ... Once AIDS developed in patients receiving early therapy, more of them tended to have multiple AIDS diagnoses, a slightly higher proportion died, and the median survival time was slightly shorter than in similar patients who received late therapy.

None of the asymptomatic individuals was receiving zidovudine[AZT]. The CD4 count of patients receiving zidovudine was lower than that of those not receiving the antiviral (mean of 69 and 217/cubic-mm, respectively) ... CD4 numbers were significantly lower in patients who developed HIV-related malignancies while receiving zidovudine


after starting antiretroviral treatment ... the estimated probability of developing lymphoma ... by 36 months, [was] 46.4% (CI, 19.6% to 75.5%) ... a direct role of therapy itself cannot be totally discounted ... Zidovudine can act as a mutagen


**Lack of Effectiveness ... and Toxicity**

Although AZT is commonly described as a ‘life saving’ drug, there are some papers that show that it might be strikingly ineffective in at least some cases.

Median RNA viral load during the first week was not significantly different for children whose mothers had taken zidovudine [AZT], compared with those in the placebo group.


Antiretroviral therapy may be initiated early during antituberculosis therapy in HIV-infected patients with tuberculosis. After initial clinical improvement, paradoxical worsening of disease developed in up to 36% of these patients, characterized by fever, worsening chest infiltrates on radiograph, and peripheral and mediastinal lymphadenopathy ... In contrast, only 7% of patients who received antituberculosis therapy but not antiretroviral therapy had paradoxical reactions.

The risk for developing AIDS among individuals in the ISS [Italian Seroconversion Study] cohort was less than 50% by 10 years after HIV seroconversion ... The relative hazards of developing AIDS in patients who started treatment with zidovudine (AZT) monotherapy was 0.57 [i.e. people starting AZT were only 57% as likely to have AIDS within the first year as others] and 0.92 within the first year and after 1 year from AZT initiation [indicating that the benefit of AZT was short term]


for the most extensively used drug, [AZT], whereas phosphorylation to the monophosphate is facile, the product is a very poor substrate for the next kinase in the cascade, thymidylate kinase. Because of this, although high concentrations of the monophosphate can be reached in the cell, the achievable concentration of the active triphosphate is several orders of magnitude lower. [Note that triphosphorylation is necessary for AZT to be active against HIV]


A total of 21 of the [125] HIV-1-infected participants died of HIV-related causes during the 3.5-year longitudinal study. Subclinical malnutrition, vitamin B12 deficiency, zinc deficiency, and selenium deficiency over time, but not zidovudine [AZT] treatment, were shown to each be associated with HIV-1-related mortality independent of CD4 cell counts <200/mm3 at baseline, and CD4 counts over time. [i.e. AZT did not reduce the risk of death]


[AZT may] unmask silent opportunistic infections ... Lack of strong evidence exists for sustained immune reconstitution by current therapies ... If [immune reconstitution] does not occur with time, despite prolonged
viral suppression, then the case for immunorestorative strategies ... could be justifiably explored [duh].


The long-term consequences of in-utero and infant exposure to zidovudine [AZT] are unknown. The long-term effects of early or short-term use of zidovudine in pregnant women are also unknown ... The incidence of adverse reactions [to AZT] appears to increase with disease progression, and patients should be monitored carefully, especially as disease progression occurs. [i.e. AZT does not prevent progression to AIDS]

Retrovir (in *Compendium of Pharmaceuticals & Specialities*). Canadian Pharmaceutical Association. 1997;1357-61

The transient effect of zidovudine [AZT] on CD4 cell counts and disease progression may have already ended in patients who used antiretroviral agents before (median time, 22.7 months) the start of TMP-SMZ [strong antibiotics] prophylaxis [or maybe the side effects left the patients weakened, and likely to experience the side effects of TMP-SMZ]


The comparison of the two studies [one European, one French] ... is interesting. Despite the wider and earlier use of zidovudine [AZT] monotherapy in the French study, morbidity or mortality was similar to that in the ECS [European Collaborative Study]. This is further indirect evidence of lack of benefit from long-term zidovudine monotherapy


Overall, zidovudine treatment was associated with only a small reduction in circulating levels of plasma RNA ... Explanations need to be considered for the apparent lack of association between the observed RNA levels and the effect of zidovudine treatment [i.e. lower rates of
transmission from mothers on zidovudine to their children cannot be due to lower levels of virus!]


[in these clinical trials] it was often difficult to distinguish adverse events possibly associated with administration of Retrovir from underlying signs of HIV disease or intercurrent illnesses [i.e. AZT can cause AIDS-defining illnesses]

Retrovir in *Physicians’ Desk Reference*. 1996

The Concorde trial showed no difference in the survival rates for symptom-free HIV-positive individuals between those given immediate and those given deferred zidovudine, and Chaisson et al found previous use of zidovudine to be a negative indicator, with an increase in the risk ratio for death or disease progression of 1.7


AZT can be severely toxic, and there is compelling evidence that the drug probably doesn’t help infected people live longer unless they already have full-blown AIDS ... AZT clearly isn’t a very effective anti-AIDS drug.

Cohen J. Fulfilling Koch’s Postulates [and several others]. *Science*. 1994 Dec 9;266:1647

the efficacy of zidovudine in preventing HIV infection after initial exposure remains unproven


The median CD4 lymphocyte count did not differ in the 3 groups: 54 for the group receiving neither antiretroviral nor P. carinii pneumonia prophylaxis, 53 for the group receiving only antiretroviral therapy, and 52 for the combined treatment group. There were also no major differences in the median CD8 lymphocyte count of the 3 groups ... Other illnesses now have elevated incidence rates among persons receiving P. carinii pneumonia prophylaxis [and AZT or didanosine]: M. avium complex,
nonretinitis cytomegalovirus disease, cytomegalovirus retinitis, candida esophagitis, and wasting syndrome


Patients who received zidovudine [AZT] before diagnosis [of AIDS] had a significantly lower CD4 cell count at diagnosis than patients who did not ... improved survival [over time, including 1987 when AZT was approved for use] was significant only for patients diagnosed with P carinii pneumonia [if AZT really had anti-HIV activity it should be effective against all AIDS-defining diseases] ... Overall survival was significantly shorter for patients who received zidovudine before diagnosis, although the survival for these patients within the first year after the diagnosis tended to be better compared with patients who did not receive AZT


When considering patients treated with zidovudine[AZT], the death rate was substantially lower within the first year after initiating zidovudine than the death rate in patients who had never taken the drug. Patients in their second year after starting zidovudine treatment experienced a death rate similar to that observed for patients who had never taken zidovudine. In the third and fourth years after starting zidovudine, the death rate was substantially greater [2-3 times higher in the fourth and fifth years] for zidovudine-treated patients than for patients who had never taken zidovudine

Lundgren JD et al. **Comparison of long-term prognosis of patients with AIDS treated and not treated with zidovudine. AIDS in Europe Study Group. JAMA.** 1994 Apr 13;271(14):1088-92

The average time with neither a progression of disease nor an adverse event (symptom or laboratory finding) was 15.7, 15.6, and 14.8 months for patients receiving placebo, 500 mg of zidovudine, and 1500 mg of zidovudine, respectively. The incidence of severe symptoms was 13.8% in the placebo group, 15.2% in the 500-mg group, and 19.9% in the 1500-mg group. After 18 months, the 500-mg group gained an average of 0.5
month without disease progression, as compared with the placebo group, but had severe adverse events an average of 0.6 month sooner.


Despite continuous antiviral therapy, the favorable effect of AZT [on viral load, not health] was typically lost within 4-6 months after treatment initiation [Table 1 shows that 5 of 7 people with disease progression took AZT, but none of 11 without disease progression]

Saksela K et al. Human immunodeficiency virus type 1 mRNA expression in peripheral blood cells predicts disease progression independently of the numbers of CD4+ lymphocytes. *Proc Natl Acad Sci U S A*. 1994 Feb 1;91(3):1104-8

Given that it is widely believed that the effect of zidovudine is of limited duration, a suggestion that the benefit lasts more than two years should be supported by the demonstration of a statistically significant difference in risk between zidovudine and placebo when one considers only the number of person-years at risk after two years of treatment. The small number of patients with end points after more than two years of therapy [in the study being commented on] makes it doubtful that such a significant difference was present. Therefore, the assertion that zidovudine has a beneficial effect that lasts for more than 2 1/2 years in these patients is not justified on the basis of the results presented.


Early treatment [before any AIDS-like symptoms] with zidovudine [AZT] is expensive and is very sensitive to the cost of zidovudine and to potential reductions in quality of life of patients who experience side effects.


the high level of plasma virus observed by Piatak et al, was about 99.9 per cent non-culturable, suggesting that it was either neutralized or defective.
Therefore, rather than supporting a cytopathic model, this observation actually may help explain the relatively slow dissemination of the infected cell burden and thus the relative ineffectiveness of therapy with nucleoside analogues which target this process.


Some HIV-infected individuals have remained healthy for more than 15 years following seroconversion. Lower numbers of CD4+ peripheral blood lymphocytes have generally been found to indicate the advancement of HIV disease ... [but] The CD4+ cell counts vary from day to day and laboratory to laboratory, and similar levels do not necessarily reflect the same disease status in all patients. For example, very low CD4+ cell counts (less than 0.05x10**9/L (50/microL)) usually indicate advanced disease; however, some patients with these levels remain asymptomatic for extended periods of time while others succumb rapidly ... While knowledge of the clinical use of zidovudine has increased during the last several years, the panel was concerned overall by the drug’s limited effectiveness and durability of response.


in individuals with fewer than 400 CD4 cells per cubic mm, those treated with AZT for longer than 16 months had the same levels of plasma [HIV] RNA as a similar group of patients who never received antiretroviral therapy.


The large Anglo-French Concorde randomized trial of zidovudine in asymptomatic HIV-infected individuals shows that there is no significant clinical benefit in terms of survival or disease progression to AIDS or AIDS-related complex (ARC) in those who started zidovudine immediately rather than those who waited for the onset of symptomatic disease. The 1749 participants were followed up for an average of 3 years.
while zidovudine [AZT] and P. carinii pneumonia prophylaxis may have been widely available to insured AIDS patients as early as 1987, cases in men who reported sex with men plateaued in late 1986, before the availability of zidovudine. This pre-zidovudine leveling has been previously reported for AIDS-related mortality in New York City.


signs of a progressively increasing level of HIV-1 activity were evident, regardless of antiviral therapy [AZT in 7 patients].


Replication curves and cytopathic effect of a standard inoculum (1 ng of p24) of 66 primary HIV-1 isolates were similar regardless of the clinical stage of the patient ... There was no difference between viruses derived from patients sensitive to zidovudine and those derived from patients resistant to zidovudine


In early 1989, 10 of the 13 patients receiving high purity [blood clotting] concentrate and 6 of 8 patients treated with intermediate purity concentrate were given zidovudine [AZT], 500 mg per day. After 1.5 years of treatment, CD4 counts were virtually unchanged (high purity, 351+/-165; intermediate purity, 179+/-178) ... [apart from one patient] the others remained asymptomatic


Doubts may be raised about the long-term beneficial effects of zidovudine treatment on AIDS-related cognitive impairments

treatment with ZDV[AZT] does not decrease the levels of HIV DNA in PBMCs [peripheral blood mononuclear cells]


thirteen subjects of 146 tested (9%) who were negative for HIV antigen [although positive for HIV antibodies] before treatment later had detectable levels of antigen during the 128 weeks of treatment [huh? AZT makes you HIV-positive?]


zidovudine monophosphate concentrations peaked at 1.3µM [1,300 nM] at 2h ... diphosphate concentration was on average 18-fold lower ... triphosphate peaked 4h after initiation of therapy at 14.5nM [without triphosphorylation, AZT cannot be effective against retroviruses, and this shows that only about 1% of AZT ever is]


In the placebo-controlled trial [of AZT], CD4 cell counts increased for four to eight weeks following the initiation of zidovudine [AZT] therapy. Following this initial increase, CD4 counts gradually diminished through week 24, at which time on average they stabilized at entry values.


**AZT and Mitochondria**

*Mitochondria are the energy regulating organelles in every living cell. Because they are self-replicating and therefore have their own DNA*
they are susceptible to damage from drugs (such as AZT) that interfere with DNA replication (mitosis). In fact, they are more susceptible, because they don’t have the same repair mechanisms as the DNA in the cell’s nucleus. Symptoms of mitochondrial damage are varied, but often include muscle damage, as the ability of the cells to obtain energy is diminished.

In umbilical cords from 6 of 9 infants born to HIV-1-infected mothers taking Combivir moderate to severe mitochondrial [mitochondria are the essential energy regulating organelles found in every living cell] morphological damage was observed, while none of 7 unexposed infants showed similar damage. Compared to unexposed infants, statistically significant mtDNA [mitochondrial DNA] depletion was observed in umbilical cord and cord blood from drug-exposed infants.

Divi RL et al. *Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir*. AIDS. 2004 Apr 30;18(7):1013-1021

AZT causes mitochondrial DNA chain replication termination in vitro [in lab systems], possibly by the inhibition of DNA polymerase-gamma, it has been theorized that AZT inhibits cardiac [heart] mitochondrial DNA replication in vivo [in the body]


**AZT and Pregnant Women and Children**

*AZT is the main drug prescribed to reduce HIV transmission from mother to child. One study showed that this reduction was from 25% (placebo) to 8% (AZT). Other studies have showed widely varying results, and some have showed transmission as high as 25% with AZT. The long term health consequences of HIV transmission versus exposure to AZT are not known. However, these references show that there is room for concern.*

Zidovudine [AZT] administered during the perinatal period may result in a small but significant and durable effect on hematopoiesis [blood production] up to the age of 18 months.
Le Chenadec J et al. **Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants.** *AIDS.* 2003 Sep 26;17(14):2053-61

An exhaustive study in a large prospective cohort with predetermined algorithm of the unexplained symptoms compatible with mitochondrial dysfunction. A total of 2644 of 4392 children were exposed to antiretrovirals ... All the children with ‘established’ or ‘possible’ mitochondriopathy [mitochondrial damage] diagnosed in this study had been exposed to antiretroviral drugs. One of these children was treated with zidovudine [AZT] only during the prenatal period and received no treatment after birth ... For the other children, the treatment was administered in the pre, peri and post-partum periods. It was zidovudine alone in five cases, a combination of zidovudine-lamivudine in 14 cases and another combination in one. 20 of the mothers received zidovudine by intravenous perfusion during labor.

Barret B et al. **Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort.** *AIDS.* 2003 Aug 15;17(12):1769-1785

children of HIV+ mothers are at risk for mitochondrial damage [mitochondria are the energy regulating organelles essential to every living cell, and that have their own DNA] that is further increased in infants of mothers receiving AZT during pregnancy

Poirier MC et al. **Long-Term Mitochondrial Toxicity in HIV-Uninfected Infants Born to HIV-Infected Mothers.** *J Acquir Immune Defic Syndr.* 2003 Jun 1;33(2):175-183

A total of 38 subjects were enrolled from June 1997 through June 1999 [1 was later excluded] ... Zidovudine was generally well tolerated in this high-risk population. The percent of patients who had selected adverse events is shown in Table II [32%-Anemia grade >=2; 11%-Neutropenia; 13%-Thrombocytopenia; 45%-Received transfusion; 26%-Received erythropoetin; 11%-HIV infection; 8%-Died] Slightly more than half of the subjects had anemia severe enough to require a transfusion [giving new meaning to the term ‘well tolerated’] ... Three infants (8%) died at 3, 23, and 31 weeks of age. All 3 were born at 26 weeks’ GA and each death was thought to be related to a complication of prematurity

Capparelli E et al. **Pharmacokinetics and tolerance of zidovudine in preterm infants.** *J Pediatr.* 2003 Jan;142(1):47-52
In our study, we found a slightly higher risk for disease progression among ZDV[AZT]-exposed, HIV-infected children during the 18-month follow-up period [as compared to HIV-infected children whose mothers were given a placebo], although this difference was not statistically significant.


[Table 3 shows that congenital abnormalities occurred in 7% of infants when both mother and child had the long course of AZT (long-long), and only 1% when both had the short course (short-short). Neutropenia and leukopenia occurred in 7% of infants on the long-long course and 2% on short-short. Infections or other HIV-related events occurred in 43% on long-long and 33% on short-short. Neonatal or other obstetrical events occurred in 22% on long-long and only 14% on short-short. Number of deaths, severe anemia were similar (although severe anemia occurred significantly less (0%/1%) in the long-short and short-long treatment arms). Mothers who received the long AZT treatment had a higher rate of stillbirth (8% vs. 4%), severe anemia (7% vs 4%), infection or other HIV events (20% vs 17%), events related to pregnancy or delivery (24% vs 17%) than mothers who received the short course, although fewer died (3% vs 8%)]


Other factors associated with lower cumulative survival included suppressed CD4 cell counts, a history of zidovudine therapy [Table 1 shows that children who had taken AZT had a 37.5% risk of death over the study period versus 22.8% for those who had not. There was a 97% probability that this increase was not due to chance], and Pneumocystis carinii pneumonia diagnosed before the initial echocardiogram.


Infants with early positive HIV-1 cultures demonstrated a notable decrement in neurodevelopmental functioning within the first 30 months
of life. They achieved motor developmental scores that were increasingly and significantly discrepant [worse] both from the average and from scores achieved by late HIV-1-positive children over the course of the study period. Those children with early HIV-1-positive cultures also demonstrated a trend toward a similar decline in mental functioning over time ... The mothers of infants with early [HIV] positive cultures were more likely to receive ZDV [AZT] treatment during pregnancy, and their infants were more likely to receive ZDV treatment prophylactically during the first 6 weeks of life ... Because antiretroviral therapy has been shown to improve neurodevelopmental function in children whose CNS has been affected by the HIV-1 virus ... Infants with early HIV-1 culture positivity should be treated with multiple drugs with well-established CNS penetration to reduce the likelihood that resistance will develop in the CNS compartment [translation: this study showed that one drug may negatively affect neurological development, so multiple drugs must do the opposite!]


In a multicenter observational cohort study of 325 HIV-infected children born during 1986-1997, clinical progression was compared among infected children exposed or unexposed to Zdv [AZT] during prenatal and perinatal periods. Zdv exposure was associated with 1.8-fold (95% confidence interval, 1.02-3.11) increased risk of progressing to AIDS or death after adjusting for year of birth, maternal CD4 cell count, maternal AIDS diagnosis, and subsequent antiretroviral therapy of the child. Mean log10 viral copies at 712 weeks were higher among Zdv-exposed children (P = .004).


Children of study women who were prescribed ZDV [AZT] had increased adjusted odds of any anomaly (adjusted odds ratio [OR], 1.55; 95% CI, 1.01-2.29) [i.e. more than one-and-one-half times the risk of a birth anomaly than the HIV+ population being studied in general] ... The prevalence of major anomalies in the full cohort based on definition 1 was significantly higher than that observed in the general New York State population ... the SMR [Standardized Morbidity Ratio] adjusted for race,
gender, and location suggests that the risk of a major anomaly in the study cohort was 2.79 times greater than the general population ... the lack of data on potential adverse effects of this therapy is still a concern ... we compared anomaly rates of subgroups defined by ZDV exposure history within the cohort of HIV-infected mothers. Babies whose mothers had ZDV exposure during pregnancy had a greater incidence of major malformations than those whose mothers did not.


Objective: To investigate zidovudine prophylaxis with caesarean section to reduce mother-to-infant HIV transmission. Interventions: Elective caesarean section before labour, usually at 36–38 weeks of gestation, plus a short oral course of zidovudine, normally starting at week 32, intravenous zidovudine before caesarean section and for 10 days for the neonate (the reduced Berlin regimen).

Results: Of 179 mother–infant pairs 104 received no antiretroviral prophylaxis or therapy (control group), 48 received the reduced Berlin prophylaxis regimen, 18 received combination therapy and nine received only part of the prophylaxis regimen. Of the antiretroviral group, 68 were delivered by elective caesarean section. The HIV transmission rate was zero in the antiretroviral group [95% confidence interval (CI) 0–4.7] and 12.6% (6.4–19.0) in the control group. The reduction in vertical transmission was 90% for the Berlin regimen, with an 80 and 70% reduction in risk associated with antiretroviral treatment and caesarean section, respectively. Maternal CD4 cell count but not viral load had some confounding effect on the reduction in risk attributed to caesarean section and the prophylactic regimen. Neonatal haematological abnormalities associated with antiretroviral intervention lasted for up to 7 weeks. Weight and length, although significantly lower at birth, were normal by 6–8 weeks.

Conclusion: A much reduced three-arm regimen of zidovudine prophylaxis in combination with caesarean section before labour is highly effective in reducing the risk of vertical HIV transmission and is safe for the infant.

Grosch-Wörner I et al. *An effective and safe protocol involving zidovudine and caesarean section to reduce vertical transmission of HIV-1 infection. AIDS.* 2000;14:2903-11
In the United States each year approximately 7000 pregnant women infected with the Human Immunodeficiency Virus (HIV-1) are treated with Highly Active Antiretroviral Therapy (HAART), either for their own disease or to inhibit maternal-fetal viral transmission. The HAART combinations of drugs typically include two nucleoside analogs and a protease inhibitor, and the nucleoside analogs zidovudine (AZT) and lamivudine (3TC) are used most frequently in combination in human pregnancy. Originally (1994) the CDC recommended that AZT be given orally for the last 6 months of pregnancy, by infusion to the mother during labor, and orally to the infant for the first 6 weeks, as standard-of-care for inhibition of vertical HIV-1 transmission.

In 1997 AZT was reported to be a moderately-strong transplacental carcinogen in offspring of pregnant mice given the drug during the last week of gestation. Drug-induced tumor incidences in lung, liver, reproductive organs and skin from mice at 1 year of age were 2-8-fold higher than those observed in unexposed controls. Incorporation of AZT into nuclear and mitochondrial DNA (7.7-100.9 molecules AZT/106 nucleotides) of liver, lung and skin, and shortened telomeres in lung, brain and liver, were found at birth in mice exposed in utero to tumorigenic AZT doses. In addition, HPRT somatic mutation frequencies in spleen and thymus of similarly-exposed mice necropsied at 15 days of age increased in a dose-related fashion.

Subsequent modeling of human exposures in pregnant Erythrocebus patas monkeys, using human equivalent protocols for AZT or the combination AZT/3TC, demonstrated that full-term fetal monkey organs contained AZT-DNA levels higher than those found in the mouse tumor study. In addition, the combination of AZT/3TC, given for the last half of the patas monkey gestation, caused both drugs to become incorporated into fetal organ DNA and to shorten telomeres in almost every fetal organ examined. Based on animal studies and in vitro indicators of genotoxicity, the International Agency for Research on Cancer declared AZT a ‘possible human carcinogen’.

In order to explore transplacental nucleoside analog genotoxicity in human pregnancies we have examined cord blood leukocyte DNA from infants of HIV-1-infected women taking AZT or AZT/3TC. We found that 68% of infant cord blood leukocytes (n=22) were positive for AZT-DNA incorporation, with positive values ranging from 22 to 451 molecules of AZT/106 nucleotides. In addition, a correlation was found between AZT-DNA incorporation and levels of intracellular AZT-triphosphorylated metabolite in cord blood leukocytes from 9 infants.

Mutagenesis, presumed to be a consequence of AZT-DNA incorporation, was examined in infant cord blood leukocytes at the glycophorin A
(GPA) and HPRT loci. The mean frequency of GPA N/N somatic mutant variants in umbilical cord blood erythrocytes was 2-3 fold higher in infants exposed in utero to AZT or AZT/3TC (n=27), compared to unexposed infants in the same study (n=30) or literature values for newborns (n=156). Infants exposed to AZT alone had half the induced N/N mutant frequency as infants exposed to the combination AZT/3TC

The HPRT mutant frequency in cord blood lymphocytes of 66 unexposed children was half that of 37 children exposed to the combination of AZT/3TC, and sequence analysis indicated that the formation of single-base transversion substitutions was >2-fold higher in the treated group. HPRT mutant frequency increases with age in unexposed populations, and the mean mutant frequency of newborns in the AZT/3TC group was similar to that seen in adolescents, while ~30% of these infants had values comparable to adults. At 1 year of age, 30% of children exposed in utero to AZT/3TC (n=18) had HPRT mutant frequencies similar to values reported for children 6-17 years, while unexposed children (n=17) had mutant frequencies comparable to children < 6 years of age.

[Conclusions] Overall, the data indicate that children of HIV-1-infected women, exposed in utero to nucleoside analog drugs, may sustain significant genotoxic insult and should therefore be subjected to long-term surveillance.


After adjusting for prematurity and maternal clinical characteristics, RPD [rapid disease progression] was three times more likely to occur in infants born to [mothers] treated [with AZT] compared with findings in untreated mothers (RR=2.8; p = .021).


All women [in this study] received oral zidovudine [AZT] prior to delivery and/or intravenous zidovudine at delivery ... Of 42 subjects ... 24 had a CVL [cervicovaginal lavage] taken ... Of these 24 women, 7 transmitted HIV-1 to their infants and 17 did not ... In the CVL samples, 41% yielded culturable HIV-1, 67% were PCR positive for proviral HIV-1 DNA, 30% were positive for cell-free HIV-1 RNA and 45% were positive for cell-associated HIV-1 RNA. Peripheral CD4 cell counts did not correlate with levels of HIV-1 in the CVL by DNA or RNA PCR or
by amount of genital tract inflammation ... Although all subjects in our study received zidovudine therapy in the third trimester, the high rate (29%) of HIV-1 perinatal transmission in this data set does not agree with the largest prospective, randomized study addressing this question, ACTG 076 [in fact, this rate is higher than the transmission rate in the placebo arm of ACTG 076]


Eight children with mitochondrial dysfunction were found ... the first patient presented with visual impairment ... [and] died aged 13 months because of respiratory and cardiac-rhythm disorders ... The second patient, from age 4 months until death at 11 months, had refractory epilepsy and deterioration of cognitive and psychomotor abilities ... At age 8 months ... patient three had a seizure ... At age 4 years, the child’s cardiac function was normal, but moderate muscular deficit persisted ... In the fourth patient ... between ages 14 and 27 months, the child had four episodes of febrile seizures ... From age 7 months until 15 months, patient five had repeated seizures ... at age 16 months ... large necrotic lesions of the [brain] ... At age 3-1/2 years the child had severe sequelae and microcephaly [abnormally small head]. Patient 6 was symptom-free until age 14 months, but persistent biochemical abnormalities were seen on standard follow-up ... Patient 7 was symptom-free until age 4 months, at which time he became hypotonic [low muscle tone] [and stopped breathing] ... The eighth child was symptom-free. Persistent hepatic and pancreatic abnormalities were seen from birth ... At age 20 months, biological abnormalities persisted ... electroretinography ... was abnormal, and cerebral NMR imaging ... showed abnormalities of the periventricular white matter ... No child was infected with HIV-1 [but because their mothers were HIV-positive] all children were treated after birth with zidovudine [AZT] alone or with zidovudine and lamivudine [3TC, also a nucleoside analogue]. Treatment continued for 6 weeks in four children and was stopped prematurely because of haematological or biochemical intolerance in four children ... The observation of several cases [of mitochondrial abnormalities] in a population of about 1700 exposed children [as compared with 1/5,000 to 1/20,000 in normal populations] strongly suggests an acquired mitochondrial dysfunction ... Pregnant women should be informed of the potential effects associated with these treatments during pregnancy

The UK’s Committee on Safety of Medicines has issued a warning to doctors about the risk of mitochondrial dysfunction in infants born to HIV infected mothers treated with zidovudine (AZT) to prevent vertical transmission ... The warning comes in advance of the publication of data from a French study in which it was discovered that 8 out of approximately 200 infants developed mitochondrial dysfunction following exposure to zidovudine, with or without 3TC treatment, for the prevention of vertical transmission of HIV infection.


The data show that AZT crosses the human placenta and becomes rapidly incorporated into DNA of placental tissue in a dose-dependent fashion, suggesting that even short exposures to this drug might induce fetal genotoxicity and might also inhibit maternal-fetal viral transmission.


Incorporation of ZDV [AZT] into DNA was detected in most of the samples from ZDV-exposed adults and infants. Therefore, the biologic significance of ZDV-DNA damage and potential subsequent events, such as mutagenicity, should be further investigated in large cohorts of HIV-positive individuals.

Olivero OA et al. **Incorporation of zidovudine into leukocyte DNA from HIV-1-positive adults and pregnant women, and cord blood from infants exposed in utero.** *AIDS.* 1999 May 28;13:919-25

Comparison of HIV-1-infected children whose mothers were treated with ZDV [AZT] with children whose mothers were not treated showed that the former group had a [1.8 times] higher probability of developing severe disease or severe immune suppression [2.4 times higher risk] and a lower survival (72.2% versus 81.0%).
transplacental exposure studies demonstrated that AZT is a moderate to strong transplacental carcinogen in mice ... Since AZT-DNA incorporation in human placenta occurs rapidly by 2 hr of AZT perfusion, infants exposed to AZT even for short periods of time during gestation may sustain genotoxic damage. In previous studies AZT has been shown to produce both, large scale DNA damage and point mutations ... the consequences of any fetal exposure to a nucleoside analog, in utero, remain unknown

Olivero OA et al. 3'-azido-3'-deoxythymidine (AZT) transplacental perfusion kinetics and DNA incorporation in normal human placentas perfused with AZT. Third Conference on Environmental Mutagens in Human Populations. 1999 Feb 18

these two [HIV+ babies taking AZT+3TC] died of an extremely rare disease caused by genetic damage to the mitochondrial DNA - which is found in the cell body rather than in the nucleus with the genes. One died at 11 months and one died at 13 months, both from severe brain damage. Blanche [of the French medical research institute INSERM] told the meeting that there was no proof the drugs caused the damage. But he said there was also no evidence the babies had inherited abnormalities, and HIV drugs are known to cause mitochondrial damage.

HIV drugs may show adverse effects in babies. Reuters. 1999 Feb 2

At present, data regarding the effects of ZDV use on vertical transmission rates are inconclusive and incomplete. In addition, the long-term effects of ZDV use during pregnancy and after birth on the woman and any resulting child are yet to be discovered ... the possibility has not yet been ruled out that this “risk-reducing” measure may not be effective and may prove detrimental to the health of both mother and child.

Conclusions: In HIV-infected pregnant women treated with two RTI [nucleoside analogs, of which AZT was the most common] with or without protease inhibitors, one or more adverse events occurred in 29 out of 37 women and in 14 out of 30 babies.


Similar levels of AZT-DNA incorporation were detected in peripheral blood from HIV-1-positive mothers and cord blood from their infants and tissues from newborn mice exposed to tumorigenic doses of AZT in utero. Therefore, the biologically effective dose (i.e. the amount of AZT that incorporated into DNA) was similar in both species even though the mouse daily dose of AZT was much higher than that received by humans.

Olivero AO et al. AZT, a genotoxic transplacental carcinogen in rodents, is incorporated into human fetal and maternal DNA. 2nd National AIDS Malignancy Conference. 1998 Apr 6;8

We present two cases of severe PCP [pneumocystis carinii pneumonia] in infants who were perinatally exposed to HIV [and AZT] but who were uninfected with HIV ... Both children had a transient decrease in their CD4 cell counts that was concomitant with the acute PCP episode ... A survey of healthy 4-year-old children showed that the seroprevalence of PCP was ~67%. Thus, children with PCP usually have asymptomatic infection. It has been suggested that immunosuppression allows P. carinii to progress to serious disease. The two children described herein were not significantly immunosuppressed, and it is unclear if any of the recognized antecedents (a mother with AIDS and severe immunosuppression, zidovudine [AZT] treatment, and concomitant herpesvirus infection) set the stage for PCP

Heresi GP et al. Pneumocystis carinii pneumonia in infants who were exposed to human immunodeficiency virus but were not infected: an exception to the AIDS surveillance case definition. *Clin Infect Dis*. 1997 Sep;25(3):739-40

The authors selected six patients who were HIV positive and who had requested termination of pregnancy to study the passage of zidovudine through the placenta ... 1 gram of zidovudine [AZT] was given in five doses of 200 mg each orally ... At a mean age of 17.5 weeks [into the pregnancy], samples were taken from the mothers’ blood, from the amniotic fluid and from the fetal blood ... The concentrations of [AZT] in
the [amniotic fluid] and in the fetal blood were higher or equaled those found in the maternal blood ... The drug remains contraindicated in pregnancy


Initiation of ZDV [AZT] therapy during pregnancy did not result in a significant decrease in viral load at delivery when controlling for the effect of pregnancy ... Mother-to-child transmission of HIV-1 occurred in one of 27 (4%) ZDV-treated women and in two of 16 (12.5%) untreated women.


In reviewing the frequency of birth defects in this population [of HIV+ women taking AZT during pregnancy] we noted eight birth defects (10%) out of 80 live births [and 8 spontaneous fetal losses, for a total of 17% abnormal pregnancies]


Treatment with trimethoprim-sulfamethoxazole and zidovudine [AZT] was started earlier and was more frequent among the 16 children born to mothers with class IV disease [AIDS]. At 18 months, ... 13 had received zidovudine [81%], as compared with ... 81 ... of the 130 children [62%] born to mothers with class II [HIV+, without symptoms] or III disease [swollen glands].


Children treated with zidovudine continued to have bacterial and opportunistic infections. The effect of the drug on the frequency of these events could not be assessed because of the lack of control groups ... One or more episodes of hematologic toxicity occurred in 54 children (61
percent)—anemia (hemoglobin level, <75g per liter) in 23 children (26 percent) and neutropenia (neutrophil count, <0.75X10^9 per liter) in 42 (48 percent)


The concentrations of the drug [AZT] in the liquor and in the fetal blood [of 6 aborted human fetuses] were higher or equaled those found in the maternal blood ... The drug remains contraindicated in pregnancy.


**Afterword**

Trevor Jones, director general of the Association of British Pharmaceutical Industries ... remembers the dramatic identification of the virus that causes AIDS ... ‘We weren’t looking for AIDS drugs, we were looking for compounds that would hit the DNA of bacteria, and we had made hundreds of these compounds. When Luc Montagnier and Robert Gallo discovered that AIDS was due to this virus, we just opened up our store cupboards and said: these should work, because they will hit the RNA of the virus. And they did,’ he said. ‘Since DNA is a ubiquitous part of life, compounds that act against it can potentially stop life forms like bacteria, like viruses, like humans. Of course, they can cause cancer as well, so balancing the risks is an essential part of the fascination.’ They settled on an anti cancer drug which had proved too toxic to use against cancer: it was AZT. It is now part of the cocktail of treatments that has changed life utterly for huge numbers of HIV positive people in the US and Europe. [So, AZT was too toxic for short term use as chemotherapy, but perfectly acceptable for long term use against HIV!]

Radford T. *Tomorrow’s pharmaceutical scientists will be part of the revolution*. *The Guardian*. 2000 Mar 30;5
THE REGISTRAR: MS PRECIOUS MATSOSO
MEDICINES CONTROL COUNCIL
2nd Floor, Hallmark Building
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Pretoria

Dear Ms Matsoso

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

A postscript to our letter of yesterday’s date: We’ve had trouble downloading Papadopulos-Eleopulos’s et al. papers, A critical analysis of the pharmacology of AZT and its use in AIDS and Mother to child transmission of HIV and its prevention with AZT and nevirapine from the authors’ archive online. We’ll send these papers up as soon as we have them.

Yours faithfully

ADV ANTHONY BRINK
CONVENOR AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP
THE REGISTRAR: MS PRECIOUS MATSOSO
MEDICINES CONTROL COUNCIL
2nd Floor, Hallmark Building
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Pretoria

Dear Ms Matsoso

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

Enclosed herewith are hard-copies of Papadopulos-Eleopulos’s et al. papers, A critical analysis of the pharmacology of AZT and its use in AIDS and Mother to child transmission of HIV and its prevention with AZT and nevirapine, both of which we were able to download from the authors’ online archive this morning (www.theperthgroup.com). We’ve also saved them to disc for you, for easy reprinting. Included on the disc is a PowerPoint slideshow presentation by the same authors (the writer included, as with the latter MTC paper) on the subject of perinatally administered nevirapine. Council is certain to find it helpful in grasping some of the basic problems with using the drug in maternity wards for pMTCT.

We concede that these scientific papers, which we have enclosed in their own lever-arch files, are voluminous and highly complex, and that they will take time to read and understand. Would you kindly give us an indication of how long Council needs, if the two weeks we have suggested is not enough?

Finally, please would you let us have the names of all members of Council on the subcommittee reviewing the special conditional registration of nevirapine for pMTCT, and who recently recommended AZT for administration to HIV-positive pregnant women in combination with it. In the event that it becomes necessary to litigate over this matter, it is our intention to subpoena them all for close cross-examination – in open court – on the fine points and ramifications of these critically relevant and important papers now before you. It will not be possible to
answer: ‘We didn’t know’ or ‘We didn’t understand’ without public disgrace and ridicule. Treatment Action Campaign leader Zackie Achmat’s fabulous confession in Rapport on 10 February 2001, ‘We are scientifically illiterate’, will be no excuse either.

Yours faithfully

ADV ANTHONY BRINK
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THE REGISTRAR: MS PRECIOUS MATSOSO
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2nd Floor, Hallmark Building
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Pretoria

Dear Ms Matsoso

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

We write to note an error in our second letter of 26 ultimo: We said that ‘Barret’s et al. findings (cited in reference 44) reported in the self-explanatory title, Persistent mitochondrial dysfunction in HIV-1 exposed but uninfected infants: clinical screening in a large prospective cohort were indeed confirmed by the same authors in a second paper in the same journal later in the year in December 2003’. This is wrong: it was in their August 2003 paper that the researchers reported: ‘The finding that the use of antiretroviral nucleoside analogues in the perinatal period is associated with persistent mitochondrial disease is confirmed ... a risk about 30 times higher than that in the general population.’

There was no second paper in December – the writer’s correspondent who drew his attention to the study when it came out, did so again in December, hence the confusion. Our apologies for that.

A detailed memorandum on the case against the use of AZT in pregnancy is in preparation, and we will forward it as soon as it’s complete.

Yours faithfully

ADV ANTHONY BRINK
CONVENOR AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP
24 August 2004

THE REGISTRAR: MS PRECIOUS MATSOSO
MEDICINES CONTROL COUNCIL
2nd Floor, Hallmark Building
Cnr Andries and Vermeulen Streets
Pretoria

Dear Ms Matsoso

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

In this memorandum we will be drawing Council’s attention to human and animal medical research literature, some of it very recent and some still in press, nearly all omitted from consideration in the World Health Organisation’s draft Antiretroviral drugs and the prevention of mother-to-child transmission of HIV infection in resource-constrained settings: Recommendations for use: 2004 Revision guidelines (hereinafter referred to as ‘the WHO Recommendations’), which has conclusively found and unequivocally predicts that:

(a) **AZT and AZT+3TC treatment of pregnant women in South Africa will kill, mentally or neurologically cripple, and/or otherwise seriously physically harm a number of their babies**;

(b) **Most of these babies will sustain ‘moderate to severe’ mitochondrial damage from in utero and postpartum exposure to these drugs**;

(c) **Unlike the case of thalidomide babies, the drug damage caused to babies during gestation and post-partum will not be evident at or soon after birth, and so the toxic cause will therefore be masked, because the harm that AZT and 3TC causes to foetal and neonatal mitochondria only becomes symptomatically evident in children many months after exposure – and, in the case of mostly poor black women and babies in South Africa, long after they have left hospital and have returned traceless to their communities**;
(d) Where the damage caused by AZT and 3TC is less obvious than death, complete or partial paralysis, complete or partial spasticity, blindness, repeated convulsions or mental retardation, it may result in subtler neurological damage giving rise to lifelong neurobehavioural deficits that may easily be misattributed to a range of harmful infant challenges, from the ‘very unfavourable psychological and social environments’ attending poverty, through ‘prematurity’, to other serious childhood diseases;

(e) Apart from brain and other neurological damage, pre-, peri- and postpartum exposure to AZT and AZT+3TC will also result in some cases to permanent bone marrow destruction, with potentially fatal consequences, and to cardiac muscle and other muscle and tissue damage of varying severity, that may be fatal;

(f) The combination AZT+3TC+nevirapine regimen recommended in the WHO Recommendations for administration to pregnant women will cause life-threatening and in some cases fatal diseases in some of them.

We will further substantiate our charge that the WHO Recommendations recommending the administration of AZT+3TC+nevirapine to prevent mother to child transmission of HIV (‘pMTCT’):

(a) wholly inadequately canvassed the substantial corpus of published human and animal nucleoside analogue (AZT and 3TC) foetal toxicity data published to date of issue (7 January 2004), and disregarded critically important studies;

(b) trivialised their significance where it mentioned them at all; and,

(c) grossly misrepresented the crucial significance of the final report of the French Paediatric HIV Infection Study Group (citation 44 of the WHO Recommendations, and hereinafter referred to as ‘the Barret study’, after lead author Béatrice Barret).

In this memorandum we will also draw Council’s attention to the very latest studies on the transplacental mitochondrial toxicity of AZT and 3TC for primate, human and rodent foetuses – reported in January, April and June 2004 respectively – all subsequent to the issue of the WHO Recommendations, and all of which Council evidently missed, and consequently failed to take into account, when issuing its new recommendation that in addition to nevirapine HIV-positive pregnant women in South Africa should also be encouraged to take AZT.

It will become obvious to Council on reading the new data pointed out in this memorandum that the WHO Recommendations on which it relied in
recommending the use of AZT, 3TC and nevirapine during pregnancy have been superannuated, and are now dangerously out of date.

To keep this memorandum within manageable proportions, we have not focussed on d4T, a drug proposed by WHO Recommendations as an alternative to AZT in the AZT+3TC+nevirapine regimen. The literature on d4T is less extensive than on AZT, but like AZT d4T is a nucleoside analogue and has essentially the same severe toxicities – predictably since nucleoside analogue compounds are widely used in cancer chemotherapy to intentionally poison off human cells. We might mention, however, that the WHO Recommendations’s sunny estimation of d4T as a drug good for pregnant women is not shared by the manufacturer itself:

On 2 February 2001 the New York Times reported an urgent alert issued by the European Medicines Evaluation Agency [EMEA] after seven cases of lactic acidosis – three of them fatal – had been reported worldwide in pregnant women taking the two drugs in combination [d4T (stavudine), sold by Bristol Myers-Squibb as Zerit; and ddI (didanosine), sold by BMS as Videx]. ... Echoing last month’s warning by the US Food and Drug Administration, the EMEA pointed out that lactic acidosis is a known side effect of the class of HIV drugs called nucleoside reverse transcriptase inhibitors (NRTIs). The use of this class of drugs is not recommended during pregnancy unless the potential benefit clearly outweighs the potential risks.

Although the drugs’ labels already included strong warnings that lactic acidosis could occur in any patient, the US FDA warned in a special advisory that ‘new evidence showed pregnant women have a greater chance of developing the condition’ (per Reuters report). Bristol-Myers Squibb added this warning to its labelling, and chased the change with a letter sent to fifty thousand AIDS doctors, warning them of the danger.

Reference in the WHO Recommendations to ‘reports of a small number of serious adverse effects possibly associated with exposure to ART [antiretroviral therapy] in the form of mitochondrial dysfunction (43-45), but an increased rate of serious clinical manifestations has not been confirmed by other studies (46-48)’ creates the falsely misleading impression that:

(a) the evidence concerning the potentially crippling effect of in utero exposure to AZT or AZT+3TC is doubtful and at best tenuous;

(b) only three studies suggest ‘a possible association’ between ‘serious adverse effects’ of exposure to AZT or AZT+3TC in the womb; and,
(c) subsequent studies disconfirmed tentative earlier ones.

Before we canvass the dire implications of the findings and conclusions reported in the Barret study, which the WHO Recommendations cursorily mentioned, misrepresented and effectively disregarded, it might assist if we recapitulate:

In September 1999 the French Paediatric HIV Infection Study Group published an alert in *Lancet* (citation 43 of the WHO Recommendations, and hereinafter referred to as ‘the Blanche alert’, after lead author Stéphane Blanche) in which, as the AIDS doctors summarised it in their report of the follow-up and confirmatory Barret study, they ‘described eight cases of children presenting principally neurological symptoms compatible with persistent mitochondrial dysfunction. The symptoms and biochemical abnormalities were identified several months after the exposure to antiretroviral drugs.’

But the damage wasn’t merely identified several months after the drug exposure: it only became manifest at that time among children who had hitherto appeared normal. That is, there was a time lag of many months between the drug damage and its manifestation in serious symptoms, in some cases ultimately fatal.

The ‘neurological symptoms’ – which the AIDS doctors might less delicately and more frankly have called massive brain and nerve damage – took the form of extensive cortical necrosis, cortical blindness, epilepsy and spastic quadriplegia in five children. Three further children were described as ‘symptom-free’ but had ‘severe biological or neurological abnormalities’ – portending serious health problems and misery in later life. The AIDS doctors also described findings of severely impaired energy metabolism and corresponding muscle and other cell damage, manifesting in heart muscle injury and muscle weakness generally.

The AIDS doctors accordingly concluded in their alert: ‘Our findings support the hypothesis of a link between mitochondrial dysfunction [in infants] and the perinatal administration of prophylactic nucleoside analogues.’ That is, the appearance of the permanently crippling, and in some cases fatal, mitochondrial disease observed in several children led the AIDS doctors to postulate the discomforting misgiving that the AZT or AZT+3TC that they had used on the pregnant women in their study, and on most of the children for a few weeks after their births, might be the cause of it.

In a commentary on the Blanche alert in the May-June 2001 issue of the French journal *Therapie* (56(3):261-6), entitled (in translation), *Antiretroviral agents and pregnancy: mitochondrial dysfunction and...*
nucleoside analogs, Loubeyre-Unique et al. highlighted that the brain-damaging effects of AZT or AZT+3TC will not always be as grotesquely conspicuous as those reported in the Blanche alert, and may take subtler ‘neurobehavioral’ forms:

An alert was published during 1999 by the French Perinatal Cohort: eight cases of mitochondrial dysfunction were reported among 1754 infants exposed to nucleoside analogues in utero and during the neonatal period. These eight infants were not infected by HIV. Mitochondrial toxicity of nucleoside analogues is clearly described in adult HIV patients receiving NRTI [nucleoside analogue reverse transcriptase inhibitors]. Zidovudine [AZT] (the only and the first NRTI studied) induced mitochondrial DNA dysfunction in animals (monkeys) and neurobehavioural effects in mice at a dose similar to the human dose.

Indeed so: numerous research papers have reported ‘neurobehavioural’ anomalies in rodents following experimental pre-natal AZT exposure, none of which the WHO Recommendations saw fit to mention in their approbation of AZT and similar chemicals for ingestion by pregnant women in developing countries like ours. And as we will show, the damaging effect of AZT and 3TC on foetal mitochondrial DNA has been shown in several studies not only in primates, but also in humans.

In 1997 Petyko et al. reported Learning disturbances in offsprings of zidovudine (AZT) treated rats in Neurobiology (5(1):83-5); in 1998 Applewhite-Black et al. noted Neurobehavioral and pregnancy effects of prenatal zidovudine exposure in Sprague-Dawley rats: preliminary findings in Neurotoxicology and Teratology (20(3):251-8); in 1999 Rondinini et al., of the Laboratorio di Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanita, Rome, Italy, described the Long-term effects of prenatal 3’-azido-3’-deoxythymidine (AZT) exposure on intermale aggressive behaviour of mice in Psychopharmacology (145(3):317-23); in 2000 the same core group of Italian researchers, now led by Venerosi, found Prolonged perinatal exposure to AZT affects aggressive behaviour of adult CD-1 mice, reported in Psychopharmacology (150(4):404-11); in 2001, in Teratology (63(1):26-37), the group, led as before, reported related findings following Prenatal exposure to anti-HIV drugs: neurobehavioral effects of zidovudine (AZT) + lamivudine (3TC) treatment in mice; a second paper in 2001 by the group, led by Ricceri, published in Psychopharmacology, reported Prenatal AZT or 3TC and mouse development of locomotor activity and hot-plate responding upon administration of the GABA(A) receptor agonist muscimol; in 2002 the group, led by Venerosi again, discussed Animal models of anti-HIV drugs exposure during
pregnancy: effects on neurobehavioral development in the light of the Blanche alert in *Progressive Neuropsychopharmacology and Biological Psychiatry* (26(4):747-61) – mentioning the French report of ‘severe yet few human cases of cardiomyopathy [heart muscle damage] and neurological disease likely associated with mitochondrial dysfunction in uninfected infants of seropositive mothers perinatally exposed to AZT’; in the same year, 2002, Melnick et al. made positive findings in their investigation of The effects of perinatal AZT exposure on the acoustic startle response in adult rats, reported in *Neurotoxicology and Teratology* (24(6):773-81); and the most recent study in this subject, by Levin et al., published this year in the January-February issue of *Neurotoxicology and Teratology* (26(1):65-71), returned a Neurobehavioral assessment of mice after developmental AZT exposure, in which the researchers recorded their observations of ‘subtle neurobehavioral impairments in mice after prenatal AZT exposure at clinically relevant doses’.

Hart et al. propose a mechanism by which AZT mitochondrial toxicity causes neurological damage in their paper, *Acetyl-l-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy*, still in press for publication in *AIDS* 2004, 18:1549–1560, but published online by Pubmed on 23 July 2004: ‘Nucleoside analogue reverse transcriptase inhibitors (NRTI) disrupt neuronal mitochondrial DNA synthesis, impairing energy metabolism and resulting in a distal symmetrical polynynepathy (DSP), an antiretroviral toxic neuropathy (ATN) that causes significant morbidity ...’ This results from AZT’s potent activity as an oxidizing agent, as pointed out in Papadopulos-Eleopulos’s et al. paper we sent up both in hard-copy and on CD, *A Critical Analysis of the Pharmacology of AZT and its Use in AIDS*, published as a special supplement to the prestigious academic medical journal *Current Medical Research and Opinion* in mid-1999 (archived at www.theperthgroup.com)

For those members of Council who might have forgotten their biology lessons, and so do not immediately appreciate the significance of mitochondrial damage, it bears emphasizing for the safety of generations of our country’s children, black and poor particularly, that mitochondria are intracellular organelles that generate the energy necessary for a wide range of vital cellular processes. When oxidized by a ‘mitochondrial toxin’ such as AZT (as the drug was described by Lamperth et al. in *Abnormal skeletal and cardiac muscle mitochondria induced by zidovudine (AZT) in human muscle in vitro and in an animal model*, published in *Laboratory Investigations*, 1991 Dec;65(6):742-51), mitochondria are unable to produce this essential energy, and several
secondary toxic effects follow, including mitochondrial DNA depletion and mutation.

It’s relevant to mention here that of all such ‘mitochondrial toxin[s]’, AZT is the most poisonous: in 1997, in the *Journal of Neurological Science* Benbrick et al. reported a comparative study of the **Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells** (149(1):19-25). Although they found that ‘AZT, ddI and ddC all exert cytotoxic [cell-poisoning] effects on human muscle cells and induce functional alterations of mitochondria ... AZT seemed to be the most potent inhibitor of cell proliferation’.

It follows that it would be the most potent inhibitor of foetal cell growth too: in May 1994 Toltzis et al. reported the **Comparative embryonic cytotoxicity of antiretroviral nucleosides** in the *Journal of Infectious Diseases* (169(5):1100-2). The cellular toxicity of ddI, ddC, and d4T, all AIDS drugs in the same chemical class, was compared with that of AZT, which the lead author and other researchers had already found to be ‘cytotoxic to early murine embryos both in vivo and in vitro’ three years earlier (see citation 38 of the WHO Recommendations). The experiment established that the ‘cytotoxicity of all three drugs was significantly less than with zidovudine at equivalent concentration’, which is to say that AZT was found best at killing foetal tissue.

Since the term ‘mitochondrial toxicity’ might have a dry and uninteresting ring to those members of Council who’ve never heard of it before, appended to this memorandum is an excerpt from the Blanche study, describing the earliest-detected eight children worst-affected in the drug experiment on them. It graphically details what we’re talking about. (Reading it requires a strong stomach or a hard heart.)

Although the WHO Recommendations claim, ‘Short-term ... tolerance of the ARV prophylactic regimens has been demonstrated’, it’s legion among doctors in South Africa that for most of them even a few days of AZT treatment following hypodermic needle pricks is unbearable, due to the extremely unpleasant subjective experience of the drug’s toxicity. Yet the WHO Recommendations suggest that pregnant women should take it for six months of their pregnancies – even right throughout them:

For pregnant women it may be desirable to initiate ARV treatment after the first trimester of pregnancy, that is after the period of major organ development in the fetus, although for pregnant women who require treatment or who are severely ill, the benefit of early therapy [during the first semester] would likely outweigh any potential fetal risks and therapy should be initiated in such cases.
Notwithstanding GlaxoSmithKline’s childish pretensions in its marketing motto, ‘Our global quest is to improve the quality of human life by enabling people to do more, feel better and live longer’, rather than making a killing in the business sense, irrespective of the human cost, the toxic ill-effects of AZT and similar drugs are unendurable for most people – as was found in an investigation to quantify this problem by Fellay et al., written up as the Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study published on 20 October 2001 in *Lancet* (358(9290):1322-7).

The researchers reported ‘a high prevalence of toxic effects’ in a cohort of 1160 patients on AZT and related drugs, more than two thirds of whom suffered side effects severe enough to affect treatment adherence – in other words prevent them from continuing to take the drugs as prescribed. Forty-seven per cent reported clinical problems like vomiting, diarrhoea, nausea, abnormal fat growth, mood swings, insomnia and fatigue. Blood tests revealed ‘potentially serious’ abnormalities among twenty-seven per cent. The researchers classed a ‘significant proportion’ of these adverse events as ‘serious or severe’. Kidney dysfunction and severe fatigue that were ‘probably or definitely’ due to the drugs led to some patients winding up in hospital.

And just by the way: rather than ‘enabling people ... to live longer’, AZT helps them to live shorter – as Andrew Phillips at the Royal Free Hospital School of Medicine in London and George Smith at the University of Bristol reminded their medical colleagues in a letter to the *New England Journal of Medicine* on 27 March 1997: ‘Extended follow-up of patients in one [AZT] trial, the [well-conducted, large-scale, double-blind] Concorde study [which found AZT to be useless as an AIDS drug], has shown a significantly increased risk of death among the patients treated early.’ Needless to say, you don’t see this mentioned in GlaxoSmithKline’s package insert.

As might be expected, pregnant women find the drugs as hard to take as Fellay et al. found people generally do. In 1998 in *AIDS* (12:F241-247) Lorenzi et al. reported Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects: ‘... 29 out of 37 women and ... 14 out of 30 babies [suffered] one or more adverse events.’ Reuters Health synopsized the trouble:

Following combination antiretroviral therapy administered during pregnancy, most HIV-positive mothers and about half of their children developed one or more adverse events. Of thirty babies, ‘the most common adverse event was prematurity (ten infants), followed by anemia (eight infants). The investigators also noted 2 cases of
cutaneous angioma [blood vessel malformation presenting as spotty tumours], 2 cases of cryptorchidism [testicles retained within the abdominal cavity], and 1 case of transient hepatitis. Two infants ... developed ... intracerebral hemorrhage [bleeding on the brain]’ and one ‘extrahepatic biliary atresia [potentially fatal constriction of bile duct].

In contradistinction to the WHO Recommendations’s allegation that AZT is readily tolerated by pregnant women, the Blanche study cited three contrary investigations – published in *J Acquir Defic Syndr Hum Retrovir* 1995;9:401-07; *Lancet* 1994;344: 207-09 (the latter paper appositely entitled *Zidovudine for mother, fetus and child: hope or poison?)* and *Drug Saf* 1995;12:274-82 – in support of its note that ‘Tolerance of this treatment has been a concern.’ Actually, a bit more than a concern: in *Teratology*. 2000 Aug;62(2):93-9, Patterson et al. pointed out that ‘many pregnant women are unable to tolerate AZT because of toxicity’. So who’s not telling the truth?

When AZT and similar drugs make pregnant women in the developing world desperately sick, just as all the literature and the skull and crossbones on Sigma Chemical Co.’s label predicts, the WHO Recommendations advise that they be forced to stay the course:

> Adherence to ARV drugs for prevention of MTCT or treatment is of critical importance, and should be promoted from the time ARV is started, and reinforced throughout prophylaxis and/or treatment, ideally at the family and community level. Guidance should include discussion with women about the known potential adverse effects of the ARV regimen they have been prescribed and importance of adherence, so they can anticipate and know how to manage minor and/or transient side effects and do not inappropriately stop therapy. After starting ARV treatment or prophylaxis, women should be seen frequently to reinforce the need for adherence to the regimen and to assess and manage any side effects of the drug. ... When ARVs are used as prophylaxis to prevent MTCT, side effects such as ARV-associated nausea, which may compound the pregnancy-associated sickness, or fears that ARV drugs might harm the foetus, should not be considered to be a contra-indication or a reason for stopping ARV treatment.

Four years after the publication of the Blanche alert, the Barret study, which followed up a ‘large ... cohort’ of ‘2644 of 4392 children ... exposed to antiretrovirals’ conclusively ‘confirmed ... a preliminary report’ (the Blanche alert) that, as opposed to the unexposed, ‘Children exposed to nucleoside analogues during the perinatal period are at risk of
a neurological syndrome associated with persistent mitochondrial dysfunction ... a risk about 30 times higher than that in the general population.’

The WHO Recommendations, however, gave these very serious and conclusive findings just a passing mention, dishonestly representing their purport in doing so: ‘There have been reports of a small number of serious adverse effects possibly associated with exposure to ART in the form of mitochondrial dysfunction (43-45)’. (The Barret study is citation 44, the Blanche alert 43, and another definitive study by Poirer et al., discussed below, is 45.)

Reading the WHO Recommendations, ignorant of the data reported in these three studies, one would think that the safety of AZT during and after pregnancy was a sure thing: ‘The safety of ARV’s used for a limited period of time in pregnancy for the purpose of prevention of peri-partum MTCT has been demonstrated. ... The potential short-term toxicity in exposed infants, if any, is expected to be very small.’

Perhaps the WHO Recommendations’s author needs glasses, because as the Blanche alert reported, far from being ‘short-term’, the effect of foetal and neonatal exposure to AZT and 3TC is ‘persistent mitochondrial dysfunction ... months or years after the end of antiretroviral treatment’, sometimes causing brain damage that shows up in Magnetic Resonance Imaging (MRI) scans, and other serious tissue damage, fatal in some cases.

As for the WHO Recommendations’s allegation that the incidence of these ill-effects was ‘very small’, it is apparent from the Barret study that its ‘30 times higher than that in the general population’ assessment of the risk of serious mitochondrial damage and consequent brain, neurological, muscle and organ tissue injury – high enough as it is – was actually conservatively computed; and we submit that the risk of serious harm that Council threatens South African children, mostly black, mostly poor, by advocating their exposure to AZT or AZT+3TC before and after birth is very much higher indeed. In fact the AIDS doctors admitted as much: ‘The true incidence [of the risk] could be higher because additional children in the cohort have similar symptomology, and several arguments strongly suggest a mitochondrial origin for these cases.’

The number of children reported injured in the Barret study was parsimoniously arrived at in a process employing ‘restrictive criteria’, in which the majority of suspected cases of ‘196 children presenting with at least one major sign or two minor signs [of] mitochondrial dysfunction’ of the 2644 drug-exposed were eliminated, leaving a remainder of just
twenty-nine cases of mitochondrial dysfunction that the AIDS doctors considered ‘established’.

Ninety-one children, including eleven who died, were thrown off the roll of ‘possible’ injury cases, notwithstanding their exhibition of ‘at least one major sign or two minor signs on two different occasions as defined in the screening procedure’, for the reason that the AIDS doctors identified ‘another cause that could account for the symptoms and/or resulted in no suspicion of mitochondrial dysfunction for 91 children’. (The defective logic of these people leaps off the page. But then they’re AIDS doctors.)

It’s noteworthy that ‘This group of 91 cases included 11 children who died during the study period.’ Nobody thought of exhuming their remains for autopsies to determine what killed them, more especially in view of the fact that AZT poisoning frequently leaves pathologists with clear biochemical clues.

In the case of ‘61 children, the symptoms identified in the database, which were confirmed by the investigator, disappeared spontaneously: various investigations during the symptomatic period were not conclusive.’ Because they were not ‘conclusive’, they were eliminated – not monitored for the possible reappearance of their symptoms, or other ones. Without explanation, the AIDS doctors figured: ‘Complementary investigation after clearance of the symptoms was not considered justified.’ Just like that.

One would have thought that in a properly conducted investigation, no effort and no expense would have been spared in conducting the most thorough examination of every drug-exposed child possible, employing every diagnostic tool, assay, psychometric and psychomotor test available to medicine and to toxic neurophysiology and toxic neuropsychology. But the children weren’t deemed worth it – probably because, as appears from the Blanche alert, most of them were black. (As are most victims of foetal AZT poisoning in the US and European inner-cities.)

Since ‘For 15 children, complementary evaluation was not possible (child lost to follow-up, parental refusal)’, there is no way of knowing how many of them were hurt or killed. For eight more, ‘results from complementary investigations are not yet fully available and conclusions not yet possible’. What we do know is that those eight children would have exhibited ‘at least one major, or two minor signs’ of ‘possible’ mitochondrial dysfunction’ to warrant the ‘complementary investigations’.

As they excluded the children exhibiting ‘at least one major, or two minor signs’ of ‘possible’ mitochondrial dysfunction’ the AIDS doctors
admitted: ‘The diagnosis of mitochondrial disease in children is sometimes considered to be very difficult and even arbitrary. ... Only cases of “established” mitochondrial dysfunction are presented here.’ Their use of inverted commas around “possible and “established” were used to indicate the arbitrariness of the body count, and that only the most severely injured were included in the tally. This implies that many more could have been.

That the AIDS doctors weren’t at all sure about the extent of the harm they had caused, and that they may have missed many injured children, was suggested in their report:

In some children, the symptoms [of ‘toxic-induced mitochondrial dysfunction’] are very strongly expressed. In others, the symptoms are mild and only a specific and adapted program of complementary examinations can diagnose or suggest the existence of mitochondrial toxicity. ... The symptoms in the children in our study were not specific, and may therefore not have been identified as toxic effects of treatment.

The AIDS doctors also employed a surprisingly crude and imprecise method for gathering information about the harm that they had caused the children by supervising their exposure to AZT or AZT+3TC before and after they were born: ‘The attending clinician was allowed to decide the extent of these investigations: consequently the investigations performed varied with the severity of the symptoms and the clinician’s evaluation of the pertinence of the mitochondrial hypothesis.’ In other words, things depended on how clever or stupid the particular doctor was.

How many drug injury cases on the less-severe end of the spectrum were missed and therefore unaccounted for, because of this ridiculous procedure, is anyone’s guess. Presumably the ‘attending physician’ had also administered or prescribed the toxic medicine, and, if so, would naturally have been less than astute to expose as many of his medical disasters to the world as possible.

The most extreme forms of injury to the chemically-crippled children were noted in the Barret study as ‘motor abnormality’ (typically involving muscular impairment such as trouble walking, talking and hand-control), ‘repeated seizures’ (i.e. epilepsy), ‘major cognitive delay’ (i.e. mental retardation), ‘tetraplegia’ (total limb paralysis), ‘hemiplegia’ (left or right side paralysis) ‘retardation of language acquisition’ (evidencing brain damage), ‘cardiomyopathy’ (damaged heart muscle, predicting early death), ‘nystagmus’ (uncontrollable rapid movement of the eyes, evidencing brain damage) and ‘severe malaise’ (non-specific persistent ill-health and weakness, consistent with toxic chemical poisoning).
In the case of twelve children in the Barret study, cerebral MRI scans revealed brain tissue atrophy (wasting), necrosis (tissue death) and other serious abnormalities. It is noteworthy, however, that in arriving at this figure, the AIDS doctors applied a remarkably restrictive protocol for interpreting MRI brain scans of children who appeared to have sustained brain damage through pre-, peri- and postnatal AZT and AZT+3TC exposure:

All the cerebral MRI data underwent two independent expert analyses. In cases of divergent interpretations, the “least severe” interpretation was used for the final analysis of the results: an MRI that was judged to be normal by one party and to be abnormal by the other was considered to be normal, regardless of the number and severity of the abnormalities observed. If the MRI findings were considered to be abnormal by both parties, only the abnormalities observed by both were included in the analysis.

Obviously, had the AIDS doctors designed a more sensitive protocol for a higher vigilance and detection level, many more cases of visible drug-damage to brain tissue would have been recorded.

Even so, it’s important to keep in mind that it’s trite in neurology that even profound, clinically apparent neurological damage or deterioration, whatever the cause, is not necessarily manifest in any observable brain tissue anomaly. Advanced Alzheimer’s disease, for example, as discussed in the modern standard reference, the *Oxford Textbook of Medicine*, is a case in point.

As they reported the iatrogenic horror that they had wreaked on the babies upon whom they had earlier been experimenting with their poisonous chemicals, one can only wonder how much greater the scale of the harm that would have been ascertained and reported had an independent panel of scientists been convened to audit the scale of the disaster. The conservative reporting bias corrupting the integrity of the Barret study findings, as bad as they were, was inevitable, given that the self-same group of AIDS doctors who had caused the carnage with its reckless medical experiments was in charge of ascertaining its extent and human cost.

The Barret study confirming the transplacental mitochondrial toxicity of AZT for human foetuses and neonates was preceded by another one by the same group of AIDS doctors, this time led by Laurent Mandelbrot, published in the *Journal of the American Medical Association* on 25 April 2001 (285(16)2083-93): *Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1* (citation 26 of the WHO Recommendations).
Yet again, of babies born to 445 AZT+3TC treated mothers enrolled in the study, 151 children suffered ‘moderate to severe hematologic adverse events’ resulting from their exposure to the drugs, including such ‘frequent serious adverse events’ as ‘neutropenia and anemia, requiring blood transfusion in nine children and premature treatment discontinuation in nineteen. Two uninfected children died at age 1 year from neurologic complications related to mitochondrial dysfunction.’ The AIDS doctors concluded that

Lamivudine-zidovudine may be effective in preventing maternal-infant HIV transmission. However, severe adverse effects ... occurred. Thus, the role of this combination therapy in this setting is as yet unclear, and further research involving a variety of strategies is needed to definitively ascertain its utility for preventing maternal-infant HIV transmission.

That is another way of saying that however excited they were by their scintillating laboratory test results, the AIDS doctors’ enthusiasm was chilled by the deaths of the children they had killed with their drugs, or poisoned – some so severely that they needed blood transfusions (an inevitably fatal procedure in many cases). These disagreeable real-world outcomes understandably made the AIDS doctors reticent about recommending to others the drug combo they had just tried on their pregnant patients and their babies.

But the doctors hired by the WHO, in pressing the administration of AZT mixed with 3TC and nevirapine on poor women and their babies in third world countries, had no such qualms:

ZDV [AZT], 3TC and NVP are the drugs of first choice to be used to prevent peripartum MTCT. ... All three drugs can be taken twice daily and infant formulations are available. To further simply the treatment, ZDV and 3TC are available in a co-formulation, thus reducing the number of pills to be taken. ... Where available a highly potent ARV prophylactic regimen for these women would be the triple cocktail of ZDV+3TC+NVP from 32 weeks of gestation through delivery and for three days post-partum.

We pause to mention here that a few days after the draft WHO Recommendations were published on 7 January 2004, insouciantly selling the above-mentioned drugs to pregnant women in the developing world to be taken during most of their pregnancies, nevirapine manufacturer Boehringer Ingelheim issued a special safety alert in the US concerning the use of its drug in pregnancy. The English online news service AIDSmap captured it in a report on the 30th:
Boehringer Ingelheim, the manufacturer of the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (Viramune) has issued important new safety information in a letter to doctors in the US about the drug’s potentially fatal liver toxicities. Safety information contained in packets of the drug will now caution that women with CD4 cell counts above 250 cells/mm$^3$, including pregnant women, who are taking nevirapine for chronic HIV infection, have a twelve-fold greater risk of serious liver side-effects, and that these have sometimes been fatal. Liver events present the greatest risk of fatality if they occur in the first six weeks of nevirapine treatment, and are often associated with a rash. However, the risk continues after this time and Boehringer Ingelheim is cautioning doctors to closely monitor patients for the first 18 weeks of nevirapine therapy. Even when nevirapine treatment is discontinued, the manufacturer is warning that in some instances hepatic injury has continued to progress. Boehringer Ingelheim also uses its letter to remind healthcare providers that any patient taking nevirapine can experience hepatic toxicities. Because of this some doctors recommend that nevirapine-treated individuals should be monitored more often than once a month. In particular, it is recommended by some experts that liver function be monitored before nevirapine treatment is started, at the time of nevirapine dose escalation and two weeks later.

In other words, a higher CD4 cell count – read by AIDS doctors (but not by informed immunologists) like the fall of a diviner’s bones and shells as an optimistic indication of how healthy you are – predisposes you to dying of liver failure if you take nevirapine. This phosphorescent wisdom has been adopted by AIDS doctors as their latest new doctrine.

Although the WHO Recommendations punted nevirapine together with AZT and 3TC as a ‘first-line’ treatment combination to be administered during pregnancy and to babies after their births, American AIDS doctors were jolted a few months later into having different ideas. A paper about fatal and other serious Maternal Toxicity With Continuous Nevirapine in Pregnancy: Results From PACTG 1022 by Hitti et al. had bitter pills to report on 1 July 2004 in the Journal of Acquired Immune Deficiency Syndromes (36(3):772-776).

The AIDS doctors had teed off with the ‘OBJECTIVE: To compare the safety of nelfinavir and nevirapine-based antiretroviral treatment in HIV-1-infected pregnant women’, giving seventeen of thirty-eight pregnant women ‘nevirapine with zidovudine plus lamivudine’, and the rest the latter two drugs with nelfinavir in place of nevirapine. Within two to twenty-six weeks of treatment, drug toxicity caused five women in the AZT+3TC+nevirapine group – twenty-nine per cent of them – to abandon
the drugs. But it was too late for an ailing African-American woman (who had been admitted perfectly healthy into the study) after her baby was cut from her: ‘1 subject developed fulminant hepatic failure and died, and another developed Stevens-Johnson syndrome.’

With these disappointments, the study was smartly aborted. But instead of fingerling the drugs on the strength of all that had been published about their toxicities, underscored by the CDC’s ban, on the advice of the FDA, of even short-term nevirapine prophylaxis for doctors and nurses suffering needlestick injuries, the AIDS doctors brilliantly blamed the fatality and life-threatening adverse effect on the alleged unique allergic predisposition to nevirapine toxicity mentioned above: ‘Continuous nevirapine may be associated with increased toxicity among HIV-1-infected pregnant women with CD4 cell counts greater than 250 cells/microL, as has been observed in non-pregnant women.’

A month after publication of the Barret study, AIDS doctors from the same study group, this time led by Le Chenadec, reported further unpleasant findings under the title, **Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants** (*AIDS*. 2003 Sep 26;17(14):2053-61): In utero AZT exposure may lead to ‘persistent inhibition of hematopoietic stem cells [causing a] significant and durable effect on hematopoiesis up to the age of 18 months’. And as might have been expected, the authors found: ‘Combinations of antiretroviral treatments were associated with larger decreases [of hematopoietic stem cells] than monotherapy up to 15 months of age.’

Expressed in lay terms, the French AIDS doctors found that AZT and 3TC poisons off babies’ bone marrow – old hat to Sigma Chemical Co., whose AZT label has always told us: ‘TOXIC Toxic to inhalation, in contact with skin and if swallowed. Target organ(s) Blood Bone marrow. ... Wear suitable protective clothing’.

This ought not to have hit the AIDS doctors as any big surprise in any event: the potent stem-cell and general haematological toxicity of AZT reported everywhere in the medical and scientific press is surely too notorious to need labouring in this memorandum, but for any members of Council ignorant of it, or who could use a refresher in this subject, some of the published research on this score is summed up (as at 15 November 2000) in paragraphs 10 to 13 of *Debating AZT: Mbeki and the AIDS drug controversy* (appended hereto as an excerpt for easy reference), and in David Crowe’s collection of citations annexed to our second letter.

That antiretroviral drugs reach and can destroy foetal bone marrow was already known to doctors (who read their journals) by 1998: in the May issue of *Pediatric Infectious Diseases Journal* (17(5):435-436), Watson et
al. had reported **Profound anemia in a newborn infant of a mother receiving antiretroviral therapy.** The HIV-negative baby, born to a positive mother who had been treated with a cocktail of AZT, 3TC and a protease inhibitor, was found to be suffering ‘high output congestive heart failure secondary to profound anemia’. The paediatricians excluded ‘infection, nutritional deficiencies, congenital leukemia and congenital red blood cell aplasia in the child’ and naturally considered the ‘cause of the life-threatening anemia in our infant ... to be in utero erythroid marrow suppression by one or more of the antiretroviral agents administered to the mother’.

The WHO Recommendations mentioned Le Chenadec’s et al. findings about persistent anaemia in children exposed to AZT or AZT+3TC in utero and after birth (citation 37bis), but cavalierly dismissed them with the comment that their ‘clinical significance’ is ‘unknown’. In reality, it is elementary in paediatric medicine that persistent anaemia in an infant is a very serious condition indeed. It means, practically, that no matter how much he breathes, the child is unable to get enough oxygen, becomes breathless after any exertion, is constantly tired, and has poor resistance to infections. He’s chronically very pale and unwell.

And far from being of ‘unknown clinical significance’, in May 1999 Mocroft et al. reported their finding in *AIDS* 3(8):943-50 that **Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe**, confirming that ‘low haemoglobin levels were found to be ‘a strong independent prognostic marker for death’. Which is to say that the ‘clinical significance’ of persistent anaemia is that it’s ‘a strong independent prognostic marker’ for dying young. (No prizes for guessing that Mocroft et al. also ‘found that 78.2% of the patients with mild or severe anaemia at baseline had received zidovudine’.)

What the WHO Recommendations scandalously neglected to mention is that the Barret study specifically addressed the likely reasons why ‘other studies’ (in the words of the WHO), which preceded their report, had not found the ‘serious clinical manifestations’ (ibid) of nucleoside analogue foetal toxicity that they had. Barret and colleagues explained the reason:

In a preliminary report we described eight cases of children presenting principally neurological symptoms compatible with persistent mitochondrial dysfunction ... The symptoms and biochemical abnormalities were identified several months after the exposure to antiretroviral drugs. Subsequently, a review of five different US cohorts failed to identify mortality specifically linked to mitochondrial disorder, but it is important to note that the review did not address
possible symptomatology in living HIV-uninfected children. ... Children born to HIV-infected mothers, even when they themselves are not infected, may show symptoms of various types. These symptoms are often associated with easily identifiable causes, but in some cases are not readily explained. Investigators of the French paediatric study have for some years been interested in a series of symptoms, mostly neurological, of children born to HIV-infected women. The neurological symptoms include cognitive delay, behavioural disorders, motor abnormalities and convulsions. Demonstration of drug toxicity during pregnancy is not easy when the suspected event is rare and the symptoms non-specific.

Contrary to the deceptive suggestion in the WHO Recommendations that there is any lingering uncertainty about the issue, there is no question at all that exposing babies to AZT in utero will cause them some degree of permanent mitochondrial damage, from sub-clinical to fatal; and there is a wealth of research data, including some very recent papers, establishing this:

Two months before the publication of the Barret study, Poirer et al., all staff scientists at the US National Cancer Institute (hereinafter referred to as ‘the NCI group’), published a study reported in the June 2003 issue of the Journal of Acquired Immune Deficiency Syndromes (33(2):175-83 – citation 45 of the WHO Recommendations): Long-Term Mitochondrial Toxicity in HIV-Uninfected Infants Born to HIV-Infected Mothers, in which they stated their findings concerning drug-caused mitochondrial DNA damage categorically and unequivocally: ‘AZT exposure causes a persistent depletion of mtDNA [mitochondrial DNA]’ among babies exposed to AZT in the womb.

Interviewed about these findings by Reuters Health on 8 July 2003, Miriam Poirer remarked: ‘We were stunned. We thought there might be some subtle changes, but we did not expect anything so striking.’ She also mentioned that in her group’s preceding primate studies, in which monkey foetuses had been exposed to human-equivalent doses of AZT+3TC, ‘we found major morphological damage in mitochondria of umbilical cords, and depletion of mitochondrial DNA in the brain, the heart, and the skeleton’.

The primate studies to which Poirer was referring were all published in 2000, and all returned findings with the gravest negative implications for the continued use of nucleoside analogue drugs during human pregnancy. The WHO Recommendations, however, completely ignored them.

In May 2000, led by Gerschenson, the NCI group noted findings starkly conveyed in the title of their paper Fetal mitochondrial heart and
skeletal muscle damage in Erythrocebus patas monkeys exposed in utero to 3’-azido-3’-deoxythymidine, published in *AIDS Research and Human Retroviruses* (16(7):635-44). Human-equivalent doses of AZT were given to pregnant monkeys during the second half of their gestational terms. Their babies were killed at birth, after which their ‘cardiac and skeletal muscle’ tissues were structurally examined by electron microscopy and with oxidative phosphorylation enzyme assays. It was found that

At the human-equivalent dose of AZT (6 mg of AZT/kg bw), there was an approximately 85% decrease in the specific activity of NADH dehydrogenase (complex I) and three- to sixfold increases in specific activities of succinate dehydrogenase (complex II) and cytochrome-c oxidase (complex IV).

The NCI group reported that ‘a dose-dependent depletion of mitochondrial DNA levels was observed in both tissues’, and concluded: ‘The data demonstrate that transplacental AZT exposure causes cardiac and skeletal muscle mitochondrial myopathy in the patas monkey fetus’.

The heart damage and partial and complete human paralysis in children exposed to AZT and AZT+3TC in utero, observed and described in both the Blanche alert and the Barret study, is consistent with the NCI group’s ‘cardiac and muscle mitochondrial myopathy’ finding in their primate study, and indeed with the vast mass of AZT-induced human and animal mitochondrial myopathy research data, both clinical and biological, reported in the medical and scientific press – briefly overviewed (as at 15 November 2000) in *Debating AZT: Mbeki and the AIDS drug controversy* and in Crowe’s collected AZT citations.

In June 2000, led by Ewings, the NCI group reported its research into the transplacental mitochondrial toxicity of AZT for foetal monkey brains, and again announced appalling findings in the title to their paper, *Genotoxic and functional consequences of transplacental zidovudine exposure in fetal monkey brain mitochondria*, published in the *Journal of Acquired Immune Deficiency Syndromes* (24(2):100-5). Performing the same EM and enzyme assay investigations as before, this time of neonatal brain tissue, the NCI group found that ‘in fetal patas monkeys given a human equivalent daily dose of AZT during the last half of pregnancy, mitochondria in the fetal cerebrum appear to sustain moderate damage’.

Since the cerebrum controls and coordinates all voluntary activity in the body and governs the lower parts of the nervous system, these findings explain the crippling physical manifestations of brain damage among babies and children reported and described in the Blanche alert and in the Barret study.
In November 2000 two of the NCI group, Gerschenson and Poirer, published a further primate study of the mitochondrial toxicity of AZT for monkey foetuses, exposed to human-equivalent doses of the drug during the second halves of their mothers’ pregnancies, in the Annals of the New York Academy of Sciences (918:269-81) – again bluntly entitled Fetal patas monkeys sustain mitochondrial toxicity as a result of in utero zidovudine exposure. ‘The fetal tissues examined include heart and skeletal muscle, which have high energy requirements, and placenta, which is less dependent on mitochondrial integrity.’ Their study ‘demonstrate[d] that mitochondrial toxicity, evidenced by depletion in mtDNA and OXPHOS enzyme abnormalities, is manifested similarly in heart, skeletal muscle, and placenta of AZT-exposed monkey fetuses’.

In January this year, in AIDS (20(1):91-100), the NCI group, led by Gerschenson, reported their investigation of the foetal mitochondrial toxicity of AZT when combined with 3TC, in a paper entitled Mitochondrial toxicity in fetal Erythrocebus patas monkeys exposed transplacentally to zidovudine plus lamivudine. Electron microscopy examination of ‘drug-exposed fetal cardiac and skeletal muscle cells showed mitochondrial membrane compromise, mitochondrial proliferation, and damaged sarcomeres, while mitochondria in brain cerebrum and cerebellum were morphologically normal’. The drugs were found to have resulted in massive mitochondrial DNA depletion – (>50%) in heart, skeletal muscle, cerebellum, and cerebrum from drug-exposed fetuses compared to unexposed controls. Overall, the data indicate that significant mitochondrial damage was observed at birth in monkey fetuses exposed in utero to AZT plus 3TC in a human-equivalent dosing protocol.

These research findings were published in the same month as the WHO Recommendations, and like those of the NCI group’s preceding findings, their baleful implications were not considered in them.

That children exposed to even a so-called ‘short course’ of AZT in utero and after birth are liable to suffer serious permanent harm is predictable from the massive corpus of published literature on the mitochondrial toxicity of AZT resulting from adult and paediatric ingestion – a toxicity with multiple pathways, both short- and long-term, as investigated and discussed by Massini et al. in Zidovudine-induced experimental myopathy: dual mechanism of mitochondrial damage, published in July 1999 in the Journal of Neurological Science (166(2):131-40).

Exacerbating the danger of foetal toxicity is the fact that following maternal ingestion, nucleoside analogues have been found in numerous human and animal studies to readily cross the placenta, accumulating in
foetal blood and foetal tissues to concentrations equal to or much higher than maternal levels:

Hankins et al., in a study of the Transplacental transfer of zidovudine in the near-term pregnant baboon reported in the American Journal of Obstetrics and Gynecology in September 1990 (163(3):728-32), found ‘higher fetal concentrations of the medication and its metabolite’ 5'-glucuronide azidothymidine than in maternal blood.

In a Preliminary study on the transport of AZT (Retrovir-zidovudine) through the placenta (translated from French) reported in the same year in the Journal of Gynecology Obstetrics and Biological Reproduction 1990;19(2):177-80, Gillet et al. described a human study on six pregnant volunteers about to undergo elective abortions. All agreed to take AZT before the procedure. Following their abortions, levels of the drug found in their aborted foetuses were measured. The study found that ‘The concentrations of the drug in the liquor and in the fetal blood were higher or equalled those found in the maternal blood.’

Pons et al. reported alike the following year, 1991, in the European Journal of Obstetrics, Gynecology and Reproductive Biology (40(3):229-31) in their paper, Placental passage of azathiothymidine (AZT) during the second trimester of pregnancy: study by direct fetal blood sampling under ultrasound:

AZT-therapy during pregnancy is actually contraindicated. Two HIV-positive pregnant women, who were due to have an induced abortion in the second trimester of pregnancy, were treated with AZT. Blood samples from mothers and fetuses and amniotic fluid samples were taken simultaneously. AZT crossed the placental barrier in the two patients. AZT and GAZT concentrations from the two fetuses were close to those obtained in the two women and in six non-pregnant volunteers.

As the Barret study summed up what is now well established: ‘Transplacental passage of nucleoside analogues such as zidovudine or lamivudine is high and fetuses and newborns exposed, sometimes for several months, to the drugs must therefore also be exposed to their effects.’ Indeed so: numerous studies have confirmed high levels of AZT in foetal tissues after maternal treatment with the drug, but it would seem futile to recite them all here in view of the latest lunatic fad among AIDS doctors. The old medical concern, expressed in 1991 by Pons et al., cited above, that especially vulnerable unborn (and newborn) babies should not be exposed to harmful chemicals with transplacental permeability has gone out of fashion in the age of American AIDS medicine, with many
AIDS doctors now urging unblinkingly that AZT be administered directly to newborn babies for the first few weeks of their lives.


The WHO Recommendations similarly vaunt an ‘antepartum + intrapartum + postpartum ZDV+3TC regimen’ as proven most ‘effective’, citing studies claiming pMTCT benefits of ‘Long (4 weeks)’ and ‘(6 weeks)’ and ‘Short (1week) ... Post-partum infant’ treatment with AZT or AZT+3TC, but finally settle, whimsically and without any cited authority, on the prescription of ‘ZDV+3TC for three days after delivery’.

Why AIDS doctors should still be pressing AZT on newborn babies, when it has officially been found too poisonous for older children is one of the many dazzling wonders of the AIDS epoch. In a study in the US, designed by Dr Janet Englwood, and sponsored by both the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development, 839 HIV-positive children were divided into three groups and treated with AZT, ddI and a combination of both. The ‘AZT alone’ wing of the study had to be called off abruptly in February 1995 due to the ‘more rapid rates of ... bleeding and biochemical abnormalities’ exhibited by the children in this group.

On 14 February 1995 the New York Times reported Englwood’s et al. findings without mincing words: AIDS drug AZT fails completely:

In a major surprise, the drug AZT – now the standard treatment for children infected by the AIDS virus – proved so ineffective in halting disease progression that federal officials have called off part of a large study involving it. AZT, or zidovudine, also had unexpectedly high rates of adverse side effects in children, like bleeding and biochemical abnormalities, officials said Monday. ... Children receiving AZT alone had more rapid rates of disease progression, AIDS-related infections, impaired neurological development and death. The findings clearly caught health officials by surprise. AZT is widely considered the drug of choice in treating HIV-infected children and adults.

Another clinical trial involving the closely similar drug d4T, A phase I/II evaluation of Stavudine (d4T) in children with human immunodeficiency virus infection, ended just as dismally – as Kline et al. reported the following year in Pediatrics (96:247-252):
Thirty-five of thirty-seven subjects [children] experienced serious clinical adverse events, including infection (33 subjects), lymphadenopathy [damage to lymph nodes] (19 subjects), hepatosplenomegaly [abnormal swelling of liver and spleen] (15 subjects), chills and fever (12 subjects), and development of an AIDS-defining condition (4 subjects). ... Clinical adverse events of lesser severity that were reported by more than 20% of subjects included rhinitis [inflamed nasal passages] (76%), cough (70%), diarrhea (68%), rash (62%), nausea and vomiting (51%), abdominal pain (43%), anorexia [appetite suppression] (41%), respiratory disorder (38%), headache (35%), pharyngitis [inflammation of throat] (32%), pruritus [general itching] (30%), pain (22%), peripheral neurologic symptoms [loss of sensation and/or pain in hands and feet] (22%), and nervousness (22%).

Notwithstanding these findings, GlaxoSmithKline and Bristol Myers-Squibb continue to indicate AZT and d4T for kids in their package inserts, without a word about these clinical trial disasters.

The speed with which AZT reaches the foetus after maternal ingestion has been reported in many studies: Little et al. began investigating this in rodent models, and published their findings concerning the Pharmacokinetics of azidothymidine during late pregnancy in Long-Evans rats in September 1989 in the American Journal of Obstetrics and Gynecology (161(3):732-4):

The drug crosses the placenta to reach concentrations in the placenta and fetus that are comparable to 75% and 58%, respectively, of those in the maternal serum by 2 hours after administration. By 4 to 6 hours after administration azidothymidine concentrations in the placenta and fetal liver significantly exceed maternal concentrations.

Boal et al., reporting Pharmacokinetic and toxicity studies of AZT (zidovudine) following perfusion of human term placenta for 14 hours in Toxicology and Applied Pharmacology in March 1997 (143(1):13-21) found ‘AZT readily crossed the placenta into the fetal compartment reaching equilibrium with maternal levels within 60-90 min after addition of each administration of AZT’.

The following month, reporting their study of Transplacental pharmacokinetics and fetal distribution of azidothymidine, its glucuronide, and phosphorylated metabolites in late-term rhesus macaques after maternal infusion in Drug Metabolism and Disposition (25(4):453-9), Patterson et al. noted that ‘AZT-monophosphate was detected in almost all fetal tissues examined’.
The NCI group, led by Olivero et al., investigated 3’-azido-3’-deoxythymidine [AZT] transplacental perfusion kinetics and DNA incorporation in normal human placentas in similar terms perfused with AZT and reported these findings in July 1999 in Mutation Research (428(1-2):41-7). Concerned because ‘transplacental exposure studies demonstrated that AZT is a moderate to strong transplacental carcinogen in mice [and] the consequences of transplacental AZT exposure to the [human] fetus remain unknown’, the NCI group investigated ‘the extent and kinetics of AZT transfer across the human placenta’. They reported their findings with the following warning: ‘Since AZT crosses the human placenta and becomes rapidly incorporated [within 2 hours of AZT perfusion] into DNA of placental tissue in a dose-dependent fashion, [this suggests] that even short exposures to this drug might induce [human] fetal genotoxicity.’

We should mention that we respectfully disagree with the NCI group’s finding that AZT is incorporated into foetal DNA; and that whatever the drug’s danger to human foetuses, we don’t consider the danger of incorporation into foetal DNA to be one of them. So as not to burden this memorandum with a technical discussion of the inappropriate assay that we contend was employed by the NCI group in arriving at their erroneous conclusion here, let alone the basic AZT triphosphorylation problem (which AIDS doctors haven’t ever heard about), we will provide the reasons for our dissension from the NCI group on this aspect separately, if requested. We point out, though, that it is generally accepted in medicine that AZT is incorporated into human foetal DNA after maternal ingestion/infusion (e.g. as stated in the Blanche alert); and we mention that the NCI group have published two further papers making this claim in relation both to apes and humans: Incorporation of 3’-azido-3’-deoxythymidine (AZT) into fetal DNA and fetal tissue distribution of drug after infusion of pregnant late-term rhesus macaques with a human-equivalent AZT dose. J Acquir Immune Defic Syndr. 1999 Dec 15;22(5):477-83; and Incorporation of zidovudine into cord blood DNA of infants and peripheral blood DNA of their HIV-1-positive mothers. Ann N Y Acad Sci. 2000 Nov;918:262-8.

Although the worst cases of AZT-induced mitochondrial disease in children exposed to the drug in the womb have proved fatal, or have resulted in conspicuously obvious permanent brain damage, or other serious injury – described in the Blanche alert as ‘symptom-free ... severe biological or neurological abnormalities’ – the absence of a narrow, distinct set of symptoms of mitochondrial poisoning makes it difficult to identify and diagnose – all the more so in a developing country like ours.
without a widely available first world medical infrastructure to monitor the time-bombing mess.

In *A comparison of genetic mitochondrial disease and nucleoside analogue toxicity. Does fetal nucleoside toxicity underlie reports of mitochondrial disease in infants born to women treated for HIV infection?* in *Annals of the New York Academy of Sciences* in November 2000 (918:247-61) Haas et al. made the same point:

Recent reports of mitochondrial disease in infants whose mothers were treated in pregnancy with nucleoside analogues are of concern. Chronic nucleoside analogue treatment of adults has long been known to cause mitochondrial DNA depletion with the risk of multisystem disease. Combination nucleoside analogue treatment regimens [e.g. AZT+3TC] may have the greatest risk of toxicity.

In other words, mitochondrial poisoning in utero can result in a wide array of disease conditions among children. Again the point was made in the report of the Barret study, noting that the ‘clinical expression ... of the mitochondrial toxicity of nucleoside analogues ... is highly variable, from peripheral neuropathy to severe lactic acidosis’.

As Le Chenadec et al. were also to discover in 2003 (their study discussed above), Haas’s et al. observation that the combination of nucleoside analogues such as AZT together with 3TC during pregnancy ‘may have the greatest risk of toxicity’ has been repeatedly confirmed:

The NCI group, led by Olivero, reporting the *Transplacental genotoxicity of combined antiretroviral nucleoside analogue therapy in Erythrocebus patas monkeys* in *Journal of Acquired Immune Deficiency Syndromes* on 1 April 2002 (29(4):323-9), found exactly that – noting that ‘the total DNA damage sustained by [monkey] fetuses exposed to both drugs [AZT and 3TC] was at least double that observed in fetuses exposed to ZDV [AZT] alone’.

Walker et al. found similarly, reporting in *AIDS* (16:2165-2173) in the same year, with the title of their paper pointing up their finding of *Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse transcriptase inhibitors.*

Naturally the authors of the WHO Recommendations didn’t think fit to mention any of this when recommending that pregnant women in the developing world, and their unborn and newly born babies, be given AZT and 3TC mixed.

It is crucially important to appreciate that the frequency and severity of mitochondrial damage caused to children exposed to AZT in utero is not
always immediately clinically obvious, even when it is severe, and that it may be initially clinically asymptomatic, as the Blanche alert noted – where the crippling, sometimes fatal, effects of AZT and AZT+3TC exposure in utero only became manifest among children several months after exposure.

Recent research on the subject of mitochondrial toxicity of nucleoside analogue drugs for human foetuses by the NCI group, led by Divi, which the scientists described as a ‘pilot study’, was published a few months ago in April 2004 in *AIDS* (18(7):1013-21) – subsequent to the publication of the WHO Recommendations – under the title, **Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir** (i.e. AZT and 3TC). The NCI group found that a cohort of HIV-1-uninfected Combivir-exposed infants with no clinical symptoms showed morphological and molecular evidence of mitochondrial damage. ... In umbilical cords from six of nine infants born to HIV-1-infected mothers taking Combivir moderate to severe mitochondrial morphological damage was observed ..., while none of seven unexposed infants showed similar damage.

Having regard to all the data on the mitochondrial toxicity of AZT published to date, along with findings made about the rapid transport of AZT across the placenta and its accumulation in foetal blood to equivalent or higher than maternal levels, there is no reason to doubt that the findings of Divi’s et al. pilot investigation – that two thirds of babies exposed to nucleoside analogue drugs in utero will suffer ‘moderate to severe’ mitochondrial damage – will in time be confirmed by a future large scale study.

The most recent research on transplacental nucleoside analogue foetal mitochondrial toxicity, conducted by Bishop et al., was reported online on 30 June 2004 by Pubmed, in advance of print publication in *Toxicological Science*, under the title **Mitochondrial Damage Revealed by Morphometric and Semiquantitative Analysis of Mouse Pup Cardiomyocytes Following in Utero and Postnatal Exposure to Zidovudine and Lamivudine**:

That myopathy and cardiomyopathy, related to mitochondrial damage, develop in some adults chronically treated with ZDV has long been known; recently, reports have suggested that similar adverse effects may occur in some infants exposed perinatally. Using a mouse model of human neonatal exposure, we treated pregnant CD-1 mice twice daily with doses of 75 mg/kg ZDV plus 37.5 mg/kg lamivudine throughout gestation and lactation; pups were exposed by direct
gavage beginning postnatal day (PND) 4 and sacrificed on PND 28. Hearts were removed rapidly, and ventricles were processed for electron microscopy. Morphometric and semiquantitative morphological analyses were performed on 3 micrographs from each of 3 blocks from each of 3 females and 3 males from the control and treated groups. Treated mice showed significant increases in the mean area and decreases in the mean number of cardiomyocytic mitochondria compared to controls. We observed clusters of damaged mitochondria more frequently in treated animals than in controls; damage included fragmentation and loss of cristae. These results, demonstrating alterations in cardiomyocytic mitochondria of mice exposed in utero and postnatally, may model cardiac damage reported in human infants similarly exposed to ZDV.

Even before it was licensed by the FDA as an AIDS drug in 1987, AZT had been found to be carcinogenic by FDA toxicologist Harvey Chernov in a review of numerous studies entitled Review & Evaluation of Pharmacology & Toxicology Data that he sent up in December 1986 for consideration by the licensing panel. Since local GlaxoSmithKline medical director Peter Moore is on record candidly warning much the same – ‘Long-term use of AZT [‘for more than six months’] does contain risks, including cancer’ (Mail & Guardian, 1 December 1999) – we won’t lumber this memorandum with all the published studies.

But as far back as 1997, the NCI group, particularly concerned about the potentially carcinogenic consequences of exposing human foetuses to AZT, conducted animal investigations into this, and found positively, as indicated in the title of their paper published in November that year in the Journal of the National Cancer Institute (89(21):1602-8), Transplacental effects of 3’-azido-2’,3’-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys.

Pregnant mice and monkeys were given AZT in the second halves of their gestational terms. By one year of age, the mice exposed to AZT in utero ‘exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver, and female reproductive organs’. ‘AZT,’ the NCI group accordingly noted, ‘is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice examined at 1 year of age.’ They advised accordingly: ‘Careful long-term follow-up of AZT-exposed children would seem to be appropriate.’

Having established that ‘AZT is unequivocally a transplacental genotoxin and carcinogen [and] given transplacentally to mice, benzopyrene [a known carcinogen employed in research laboratories to induce cancers]
produced lung and liver tumour multiplicities similar to those observed [with AZT], the NCI group recorded their concern that ‘the current practice of treating HIV-positive women and their infants with high doses of AZT could increase cancer risk in the drug-exposed children when they reach young adulthood or middle age’.

Only GlaxoSmithKline’s lawyers took note: on 4 March 1998, to hedge the company against damages actions arising from the development of cancers in people exposed to AZT before they were born, the ‘PRECAUTIONS: Information for Patients: Carcinogenesis, Mutagenesis, Impairment of Fertility’ section of AZT’s ‘PRODUCT INFORMATION’ was amplified; to the sentence, ‘The long-term consequences of in utero and infant exposure to Retrovir [AZT] are unknown’, was added the phrase, ‘including the possible risk of cancer’.

The subsequent appearance of cancers in children exposed to AZT in utero, just as the NCI group’s animal studies predicted, hasn’t caused any alarm among AIDS doctors who promote the drug as a perinatal anti-HIV prophylactic – due, it appears, to a typical medical mindset problem, particularly among those whose professional reputations are deeply invested in this asinine treatment. In a private note to the writer, praising the ‘good comprehensive review of the literature you performed’ in Debating AZT: Mbeki and the AIDS drug controversy, Ofelia Olivero of the NCI group remarked upon this phenomenon: ‘During my research I noticed a lot of resistance from many different people to believe our data. In general there is resistance to the “bad news”’.

This ‘resistance to the “bad news”’ is well illustrated in the case of Ellen Cooper, one of the US FDA panellists who approved the licensing of AZT as an AIDS drug in February 1987 (see the fraud spilled in Licensing AZT in the appendices to ‘Just say yes Mr President’: Mbeki and AIDS) and Principal Investigator of the Women and Infants Transmission Study (ACTG076, sponsored, like the original licensing trial, by the drug’s manufacturer) on the basis of which AZT, previously strenuously contraindicated in pregnancy by numerous authorities, is today used in pregnancy – a study meticulously analysed and completely debunked by Papadopulos-Eleopulos et al. in their exhaustive, 130 000-word Mother to child transmission of HIV and its prevention with AZT and nevirapine monograph, which we sent you in hard-copy last month. (If you’ve lost it it’s archived online at www.theperthgroup.com.)

Cooper was quoted in the September/October 1998 issue of Mothering magazine: ‘We don’t know what the long-term effects of AZT use during pregnancy might be, but so far we have seen virtually no adverse effects in the short term. ... Not one single tumor. Not one. ... I mean [the
children] have cancers, lymphomas, and other problems like that ... but there’s no reason to link those cancers to AZT.’

But given Olivero’s findings that AZT has exhibited transplacental carcinogenicity in animal models, and Pluda’s et al. discovery of the Development of non-Hodgkin lymphoma in a cohort of patients with severe human immunodeficiency virus (HIV) infection on long-term antiretroviral therapy, published in Annals of Internal Medicine, in August 1990 (113(4):276-82) – just under half of them within three years, an incidence of the disease about fifty times higher than normal – there would seem to be every reason in common sense to ‘link those cancers to AZT’.

Whether in decades to come, the ‘unequivocally’ established ‘transplacental genotoxicity and carcinogenicity’ of AZT in animal models likewise manifests among human adults exposed to AZT in their mother’s wombs, like thousands of DES victims in the first world today, remains to be seen.

The transplacental carcinogenicity of DES had been well-established in many animal studies, all ignored by medical experts and doctors lauding the drug. To quote Nora Cody speaking in July 1999 at the National DES Research Conference in Bethesda in the US: ‘30 years ago today DES was still being prescribed to pregnant women in this country and, indeed, around the world. By 1969 scientists had studied this scientific substance for over three decades. Over and over, they had found cancer in laboratory animals.’

For those girls lucky enough not to be born with deformed, virilised genitals, only when they reached adulthood did the harm the drug had caused become apparent in the form of ordinarily rare carcinomas in their vaginas and cervixes (among other problems).

It’s significant in this regard that the murine studies of the NCI group led by Olivero, reported in 1997 (discussed above), found that mice exposed to AZT in utero ‘exhibited statistically significant, dose-dependent increases in tumor incidence and tumor multiplicity in the lungs, liver, and female reproductive organs’.

The NCI group, led by Diwan, published further findings of Multiorgan transplacental and neonatal carcinogenicity of 3’-azido-3’-deoxythymidine in mice in Toxicology and Applied Pharmacology in November 1999 (161(1):82-99). Following up on their 1997 study of one-year-old mice exposed in utero to AZT,

Findings for all remaining offspring up to 2 years old are reported here. AZT effects were most prominent in female offspring, with a
significant threefold increase in lung tumors, a reduction in lymphoblastic and follicle center cell lymphomas, and a significant increase in histiocytic sarcomas (0 in controls, 3% after low-dose AZT, and 8% after high-dose AZT, p = 0.022). Dose-dependent incidences of mammary gland, ovarian, and seminal vesicle tumors were low but significant: 0/106 controls, 3/105 low-dose, and 8/105 high-dose mice presented one of these neoplasms (p = 0.0025). Incidences of females showing any clearly AZT-related neoplasm, in lung, liver, ovary, or mammary gland or histiocytic sarcoma, in the second year, were 12/32 after the low dose and 14/27 after the high dose vs 3/23 controls (p = 0.0045). Also, the sensitivity of neonatal mice was assessed by administration of 25, 50, 100, or 200 mg/kg AZT on postnatal days 1 through 8. The effects at 2 years were similar to those seen after transplacental exposure, with significant increases in lung, liver, and mammary tumors in females. The results confirm that AZT is a moderately effective perinatal carcinogen in mice, targeting several tissue types.

Another study by the NCI group, led by Bialkowska, *Oxidative DNA damage in fetal tissues after transplacental exposure to 3’-azido-3’-deoxythymidine (AZT)*, was published the following year in the May 2000 issue of *Carcinogenesis* (21(5):1059-62). Noting that ‘AZT has been found to be a perinatal carcinogen in mice’ the NCI researchers investigated possible mechanisms for this in further studies with pregnant mice and monkeys. In the case of mice they found that exposing mice foetuses to AZT (‘the transplacental carcinogenesis regimen!’) led to significant increases in 8-oxo-2’-deoxyguanosine (8-oxo-dG) ... in the livers, a target tissue for transplacental carcinogenesis, and in the kidneys. ... Tissues were also obtained from fetal patas monkeys (Erythrocebus patas), whose mothers had received 10 mg AZT/day during the last half of gestation. Although limited numbers of samples were available, possible increases in 8-oxo-dG were noted, relative to controls, for placenta and for fetal lung and brain (P = 0.055 for treatment-related increases in these tissues). These results suggest that an increase in reactive oxygen species could contribute to the mechanism of transplacental carcinogenesis by AZT in mice, and that this may also occur in primates.

Presuming that Council is even aware of the AZT transplacental carcinogenicity data canvassed in this memorandum, which we doubt, it’s hard to imagine that its members will be happy to take a wait-and-see position in regard to whether South African babies, born to mostly poor and black mothers, develop cancers in childhood and adulthood, thanks to
the AZT they have just recommended their mothers ingest while carrying them. Surely not any black members.

The administration of AZT to pregnant women and their newborn babies is justified, one reads over and over like a stuck gramophone, on the basis that it saves babies’ lives. As Blanche et al. were blanching over their sinking suspicion confessed in their ‘Early report’ in *Lancet* in 1999 that they had crippled and in some cases killed children in the most terrible way with their strong drugs, they defended themselves saying, ‘Prophylaxis of mother-to-child transmission of HIV-1 infection has saved thousands of children from death.’

But in a paper that was otherwise thoroughly referenced, there was no reference put up to support this show-stopping claim. That’s because there isn’t one to cite. Just as there isn’t one for leading American AIDS expert Lynne Mofenson’s foundational claim in September 2000 in the *New England Journal of Medicine* (343(11):803-805) in an editorial, *Perinatal Exposure to Zidovudine – Benefits and Risks*: ‘Mother-to-child transmission of the human immunodeficiency virus (HIV) causes a chronic and ultimately fatal pediatric infection …’. There’s no reference supporting that either – but the French AIDS doctors who published the Blanche alert and Barret study bought it anyway, citing the Mofenson editorial in their AZT+3TC paper discussed above (Mandelbrot et al. in *JAMA* 285(16)2083-93.)

There is no good evidence that children privileged enough to get AZT while in their mothers’ wombs, and immediately after birth for a while, do better and go on to live happier, healthier lives than children sadly deprived of it. On the contrary, when AIDS doctors are finished playing in their laboratories with all their little tests, and return to the real world in which their AZT-burned infant patients have to make their way, and they look at how the drug-treated babies have turned out, as against untreated children, they consistently find that AZT-exposed babies are very much worse off. Which is to be expected by anybody with even a fleeting familiarity with the toxic pharmacology of the drug.

That exposure to AZT in the womb and after birth leads to a higher death and serious disease rate among drug-exposed babies than untreated ones has been apparent for several years, but in the contemporary AIDS craze this has simply been disregarded:

1. In *Rapid disease progression in HIV-1 perinatally infected children born to mothers receiving zidovudine monotherapy during pregnancy*, reported in May 1999 in *AIDS*, (13:927-33) de Martino et al. reported that
Comparison of HIV-1-infected children whose mothers were treated with ZDV with children whose mothers were not treated showed that the former [AZT treated] group had a higher probability of developing severe disease (57.3% ... versus 37.2%) ... or severe immune suppression (53.9% ... versus 37.5% ...) and a lower survival [rate] (72.2% ... versus 81.0% ...).

2. In June 2000, De Souza et al. published consistent findings in *Journal of Acquired Immune Deficiency Syndromes* (1;24(2):154-61) concerning the Effect of prenatal zidovudine on disease progression in perinatally HIV-1-infected infants. Their objective was to
determine the influence of prenatal zidovudine (ZDV) prophylaxis on the course of HIV-1 infection in children by comparing the clinical outcome of infants born to HIV-1-seropositive mothers who did versus those who did not receive ZDV during pregnancy. ... The main outcome measure was rapid disease progression (RPD) in the infant, defined as occurrence of a category C disease or AIDS-related death before 18 months of age. ... Among infected infants, the RPD rate was 29.4% in the no ZDV group compared with 70.6% in the ZDV group ... The rate of RPD was five to six times higher among infants born to treated compared with untreated mothers ...

3. In July 2000, in the *Journal of Infectious Diseases* (182(1):104-11), Kuhn et al. reported likewise in their study of 325 HIV-positive children born between 1986 and 1997 until death or diagnosis with AIDS, under the title, Disease progression and early viral dynamics in human immunodeficiency virus-infected children exposed to zidovudine during prenatal and perinatal periods. Their findings were summarised in a report by Reuters Health:

Among infected children who did not receive ART before AIDS diagnosis, 44% developed AIDS or died before age 12 months when they were exposed to prenatal or perinatal zidovudine. However, among HIV-infected infants not exposed to zidovudine prophylaxis, rate of death or progression to AIDS was only 24% ... Zidovudine exposure before birth or perinatally appears to accelerate disease progression in HIV-infected infants.

4. In *Timing of perinatal human immunodeficiency virus type 1 infection and rate of neurodevelopment*, reported in *Pediatric Infectious Diseases Journal* in September 2000 (19(9):862-71) Smith et al. reported late-presenting evidence of neurological and brain damage caused by exposure to AZT in utero and after birth. As the Blanche alert had noted a year previously – subsequently confirmed by the Barret study in mid-2003 – the stultifying drug injury to the brain took time to become
symptomatically evident, and, in the study in point, only became apparent when the children were specially tested for cognitive function and performance:

Infants with early positive HIV-1 cultures demonstrated a notable decrement in neurodevelopmental functioning within the first 30 months of life. They achieved motor developmental scores that were increasingly and significantly discrepant both from the average and from scores achieved by late HIV-1-positive children over the course of the study period. Those children with early HIV-1-positive cultures also demonstrated a trend toward a similar decline in mental functioning over time ... The mothers of infants with early [HIV] positive cultures were more likely to receive ZDV [AZT] treatment during pregnancy, and their infants were more likely to receive ZDV treatment prophylactically during the first 6 weeks of life.

5. Concerning the WHO Recommendations’s advocacy of a return to long-course AZT for pregnant African women, rather than the short-course treatment that has become the fashion among AIDS doctors in recent years, the data entered in Table 3 in A trial of shortened zidovudine regimens to prevent mother-to- child transmission of human immunodeficiency virus type 1 by Lallemant et al., published in the New England Journal of Medicine on 5 October 2000 (343(14):982-91), reaffirmed the harm this causes children: a 7% congenital abnormality rate following long-course exposure versus 1% after short-course exposure; likewise a 7% neutropenia and leukopenia rate versus 2%; infections or other ‘HIV-related’ events were 43% versus 33%; and neonatal or other obstetrical events occurred in 22% versus 14% of cases. Mothers on long course AZT treatment had a higher rate of stillbirth (8% vs. 4%), severe anaemia (7% vs 4%), infection or other HIV events (20% vs 17%), and events related to pregnancy or delivery (24% vs 17%) than mothers who received the short course. Which is not to say that short-course foetal exposure to AZT is safe:

6. In support of the suggestion that AZT may safely be taken in pregnancy – ‘There have been reports of a small number of serious adverse effects possibly associated with exposure to ART [antiretroviral therapy] in the form of mitochondrial dysfunction (43-45), but an increased rate of serious clinical manifestations has not been confirmed by other studies (46-48)’ – the WHO Guidelines cite a study (citation 47) by Chotpitayasunondh et al., including staffers of the US CDC, Safety of late in utero exposure to zidovudine in infants born to human immunodeficiency virus-infected mothers: Bangkok, published in Pediatrics in January 2001 (107:E5). The happy title notwithstanding, the researchers reported a five times higher febrile convulsion rate and an
11% higher incidence of serious disease among the short-course AZT-exposed babies as compared with the unexposed. (This the AIDS doctors dismissed as ‘a slightly higher risk for disease progression among ZDV-exposed, HIV-infected children during the 18-month follow-up period, although this difference was not statistically significant.’) And as for the dishonest suggestion in the WHO Guidelines that this study was at variance with others that reported mitochondrial dysfunction among AZT-exposed babies – in the sense of disconfirming them – Chotpitayasunondh et al. specifically conceded that

our sample size was chosen to determine the efficacy of short-course ZDV and to identify adverse events that occur with high frequency; it was not large enough to detect an increased rate of adverse events that occur rarely. Also, the number of infected children is too small and follow-up too short to draw conclusions about disease progression related to ZDV exposure. Second, our review of clinical conditions potentially associated with mitochondrial dysfunction was retrospective and could not evaluate the incidence of subtle clinical findings or laboratory abnormalities that might suggest mitochondrial dysfunction. Third, as in other studies to date, our follow-up period of 18 months is too short to enable us to evaluate the incidence of conditions, such as cancer, that may take many years to develop.

7. But the striking ‘incidence of conditions, such as’ infant death following the treatment of babies and children with AZT and a similar drug, ddI, was revealed by Chotpitayasunondh himself in an interview he gave Karen Emmons for her article in the *San Francisco Examiner* on 31 May 1999:

Of the children who were born HIV-positive in Bangkok in the past four years and received the combination drug treatment, Chotpitayasunondh said that one-fourth died in their first year, about 33 percent by their second year, 40 percent by age 3, and then the mortality tapered off.

To repeat: forty per cent of the AZT-treated babies were dead before their third birthday. But to the wide-eyed American reporter, this was evidence that Thailand wins a round in fight against HIV, as she called her piece, rather than ‘An iatrogenic disaster in Thailand’.

8. The conclusion that this appalling death rate was the result of AZT (and ddI) poisoning is supported by a similar fatality tally among AZT-exposed children reported by Lipshultz et al. in *Circulation* on 26 September 2000 in their paper *Cardiac Dysfunction and Mortality in HIV-Infected Children* (102(13):1542-8): ‘Other factors associated with lower cumulative survival included ... a history of zidovudine therapy.’
Table 1 in the published report reflected that 37.5% of children given AZT died, as against 22.8% of the untreated children – which is to say that treatment with AZT almost doubled their death rate.

Yet even as they reported these brute facts, many of the AIDS doctors who conducted these studies were telling us what great stuff AZT is, and that its use in pregnancy should unquestionably be continued. They weren’t put out by their own data showing that AZT-exposed infants get sick and die at a much higher rate than unexposed ones. That AZT causes AIDS one might say. As Heresi et al. did, more or less, in September 1997 in their report in *Clinical Infectious Diseases* (25(3):739-40), describing *Pneumocystis carinii pneumonia in infants who were exposed to human immunodeficiency virus but were not infected: an exception to the AIDS surveillance case definition*: ‘We present two cases of severe PCP [pneumocystis carinii pneumonia, a classic and original AIDS-defining disease] in infants who were perinatally exposed to HIV [and AZT] but who were uninfected with HIV.’ An unremarkable turn for the worse in the babies’ health, really, since as the *The Physician’s Desk Reference* revealingly notes, ‘It was often difficult [in AZT clinical trials] to distinguish adverse events possibly associated with administration of Retrovir from underlying signs of HIV disease or intercurrent illnesses.’

And likewise, in company with De Martino, de Souza, Kuhn and fellow AIDS doctors, having just confirmed that indeed, as they had feared, AZT and 3TC cripples and in some cases kills children exposed to it before and after birth, the French AIDS doctors in the Barret study tried slapping down any worries by asserting emotively, again without authority in the shape of any controlled study, ‘It is clear that the number of children worldwide who suffer because that have not received antiretroviral treatments is inestimably larger than the number of children who suffer due to the toxicity of these treatments.’

It was the same spiel in the Blanche alert: ‘We are aware that the suggestion that antiretroviral drugs are toxic raises delicate issues.’ Which the doctors tried stilling by immediately laying their earnest claim on us that ‘Prophylaxis of mother-to-child transmission of HIV-1 infection has saved thousands of children from death.’ Except that, when clinical outcomes are considered – and not meaningless, unvalidated, non-specific blood tests (about as scientific as an apartheid Race Classification Board inspector’s pencil test) – the ‘children who suffer’ turn out to be the beneficiaries of American medicine.

The sort of canards professed by the French AIDS doctors in excusing the atrocities they had perpetrated are known in a religious context as articles
of faith; and, in the high purpose that the doctors proclaim in their healing mission against the sex-virus (especially prevalent among blacks, such AIDS doctors say), they are used to justify the violence they deploy against women and children, well knowing that it will injure many of them, as we see. Implying, though, that strong measures are called for. That a firm approach is needed with these people.

Indeed, against what US Secretary of State Colin Powell described to Larry King on 11 July 2003 as a ‘weapon of mass destruction’, formally declared ‘a threat to US national security’ by former US President Bill Clinton on 29 April 2000 (bringing the NSC and the CIA with all its internationally-situated spooks and goons into the game), ‘aggressive, effective action’ is what’s needed – so insisted former US ambassador Cameron Hume at Rhodes University on 21 October 2002.

The Barret study confirms and predicts with absolute, incontestable certainty that children exposed to AZT before birth will be injured, and in some cases killed. We wonder whether Council joins in the view expressed by the Americans, and by those white AIDS doctors in France, that the killing and maiming of mostly black, mostly poor children by ‘aggressive, effective action’ in the holy war on AIDS is acceptable collateral damage. Because we think it’s criminal and we think it’s obscene.

Especially since, as you will have read by now, the vacancy of the entire pMTCT project (just like the ‘weapons of mass destruction’ ruse for the Americans’ other neo-colonial business further north) was revealed as Papadopulos-Eleopulos et al. demolished it brick by brick in their *Mother to child transmission of HIV and its prevention with AZT and nevirapine* monograph. Did you understand it?

To be honest, we think that any member of Council who, after having read that jolly big paper, still subscribes to any of this MTCT mythology – this new American idea that mothers, mostly black, mostly poor, can kill their babies by bearing them, giving birth to them and by breastfeeding them, and that they do well from transplacental exposure to carcinogenic, mutagenic cell-poisons – really needs new batteries.

Way back in 1991 Hayakawa et al. made an alarm call, *Massive Conversion Of Guanosine To 8-Hydroxy-Guanosine In Mouse Liver Mitochondrial DNA By Administration Of Azidothymidine* in *Biochemical and Biophysical Research Communications* (176, 87-93), warning, in the light of their findings, that ‘it is urgently necessary to develop a remedy substituting this toxic substance, AZT’.
In their monumental 25,000-word examination and explosion of GlaxoSmithKline’s core claims in biochemistry for AZT as a medicine, *A Critical Analysis of the Pharmacology of AZT and its Use in AIDS*, Papadopulos-Eleopulos et al. took the same view:

A critical analysis of the presently available data which claim that AZT has anti-HIV effects shows there is neither theoretical nor experimental evidence which proves that AZT, used either alone or in combination with other drugs, has any such effect. The recommendation that AZT, either alone or in combination, is administered to HIV seropositive or AIDS patients warrants urgent revision.

Particularly because, as they point out, ‘the scientific literature ... elucidate[s] a number of biochemical mechanisms which predicate the likelihood of widespread, serious toxicity from use of this drug’.

The French AIDS doctors conducting the Barret study grudgingly conceded that it’s high time that AZT in maternity hospitals – like bloodletting, arsenic and mercury as earlier standards of medical care – should be ditched: ‘Many antiretroviral molecules of different therapeutic classes are now available and it is very plausible that certain molecules or combinations of molecules be better tolerated than others by the fetus and newborn.’ Better tolerated.

It’s just a pity that stuck in their virus/chemo rut the AIDS doctors didn’t ponder any wider alternatives to these deadly poisonous compounds, such as nutritional support for mothers fallen ill, in the form of nutrient-rich diets supplemented by micronutrients and antioxidants. Both Pubmed and the Cochrane Database lists dozens of directly relevant studies, published in the world’s leading medical journals, reporting not only the clinical benefits of micronutritional therapy for pregnant women, but also encouraging results in testing procedures that AIDS doctors think indicate MTCT.

Apart from being non-patentable, and therefore inexpensive, micronutrient preparations have the added advantage of being completely safe for both mother and child. You surely saw the Harvard School of Public Health’s big study, published last month in the *New England Journal of Medicine* (351;1), *A Randomized Trial of Multivitamin Supplements and HIV Disease Progression and Mortality*, by Fawzi et al., which turned in splendid results for everybody. What’s more it was a randomized, placebo-controlled, double-blind clinical trial, the way it was supposed to be. Which you can’t say for any AIDS drug trial, ever.
The WHO Guidelines, it should be noted, spring directly from the germ-chemotherapy paradigm of AIDS promoted by the pharmaceutical cartel, and by all those busy bees in the research industry and in academia that it supports, flying them around and lavishing grants upon them, and who in turn faithfully serve it; and they take no account of available alternatives to the aggressive use of highly toxic chemicals on developing world mothers and their unborn and newborn babies.

And more’s the pity that the French AIDS doctors didn’t share Hayakawa, Papadopulos-Eleopulos and their colleagues’ sense of urgency as they surveyed the wasteland after waging their noble battle in maternity wards in what the WHO Recommendations calls the ‘fight’ against ‘the HIV/AIDS epidemic’ – a ‘fight’ joined by a sprinkling of loyal natives such as William Makgoba (to whom we’ll return) and Kgosi Letlape, who heads the South African Medical Association, against an epidemic strangely invisible to most other Africans, other than in the drearily familiar form of diseases of poverty, which have afflicted them ever since they lost their lands. But which big-time local AIDS expert Professor Jerry Coovadia attributes, as all non-African AIDS doctors do, to the ‘unbridled sexuality’ of ‘newly independent people’ – by which he means the unique, fantastic promiscuity of the servants.

Admittedly it would have taken a lot of courage for the French AIDS doctors reporting the Barret study to have publicly repudiated their deadly medicines; and as they demonstrated, none of them were man enough for it. The question is: is Council? Alexander Pope once gave the problem an encouraging spin, however: ‘A man should never be ashamed to admit that he has been in the wrong, which is but saying, in other words, that he is wiser today than he was yesterday.’ Generations of affected South Africans, mostly black, mostly poor, will be looking back and asking: how could this have been allowed to happen? Wasn’t there anyone there to protect us?

After the lessons supposed to have been learned in the precedent thalidomide disaster, well they might wonder. But a brief review of that tragedy in the 3rd edition of the *Oxford Illustrated Companion to Medicine* explains things in terms of the characteristic constipation of the medical mind:

It was then widely believed that the human placenta was impervious to poisons except in such doses as killed the mother. Yet there was already widespread evidence that this was untrue and that fetuses could be deformed by external influences, including poisoning and therapeutic drugs ... but most of it had been ignored because this suited the contemporary mind-set or Denkstil. ... Why did the medical
profession ignore the extensive existing evidence that teratogenic substances (causing developmental abnormalities in the fetus) could cross the placenta? It is useful to look at the question as part of a mind-set or a shared view of reality that controls, organizes, and limits perception and understanding. We all tend to ignore what does not fit the theories and beliefs with which we live.

As disaster-porn, the brain damage and other crippling harm that AZT causes during pregnancy and after birth does not make such salaciously spectacular copy for the newspapers as that caused by thalidomide – whipping up public interest and sympathy, and therefore good for circulation and profits – but for the victims, their parents, their siblings and others close to them, the consequences, kicking in several months after drug-exposure, are just as horrible, just as tragic. Every minute, every hour, every day, for a lifetime.

We do understand that it is very embarrassing for doctors, pompous experts especially (and goodness, our country has enough of them), to admit that they have been mistaken – doubly so when their medicaments, ladled down with the best intentions, to gratifying public acclaim, turn out to have been harmful and sometimes deadly; but the history of Western medicine is one of grand errors, usually lasting centuries and sometimes millennia, and scarcely credible afterwards.

We trust that in the light of the data presented in this memorandum, however, Council will act robustly, and not faff around in the manner of Supreme Court of Appeal Judge Edwin Cameron, who, when confronted with the AZT toxicity data for unborn babies set before him by President Mbeki in mid-March 2000, in a fifteen-page reply to the former’s appeal for the provision of this elixir to pregnant women, told reporters that his ‘heart sank’ as he read it ‘with a sense of fear and dismay’ – not because the data appalled him as it had the President when he read an early draft of Debating AZT: Questions of safety and utility, causing him to change his mind radically about the drug, but because, it appears, he winced at owning to what a fool he had made of himself in publicly advocating the drug.

We must confess, to be frank, that, although he likes publicly to declaim that ‘I have no doubt that I have natural intellectual gifts’, we find little evidence of them in his prosecution of his pet cause. Despite being presented with the case against the use of AZT in pregnancy thrice in 2000 – by President Mbeki, African historian Professor Charles Geshekter of UC California at Chico, and this writer – he has failed to weigh it, much less apologise to President Mbeki for aspersing him repeatedly from local and foreign podia on account of his well-founded
concern over this drug – perhaps in the sort of terms in which the English novelist John le Carré framed a complimentary review of *Debating AZT: Mbeki and the AIDS drug controversy*:

I agree with (the alas late) Donald Woods: [AZT] needs much more serious debate than Big Pharma and the usual club of fringe beneficiaries are permitting. There is simply too big a case to answer, and it’s not being answered. Having said that, I suppose I look a bit of a fool because I’m one of the numberless well-intentioned people who have been championing cheapo antiretrovirals for the Third World’s afflicted etc.

We hope that unlike his lordship, Council will react rather more responsibly, and will move quickly to revoke its latest recommendations, however awkward this might be. After which, some resignations might be in order, if, in this country, ordinary principles apply to failure in public office – evidenced by Council’s disgraceful ignorance of the published literature in its field.

Council really wouldn’t be acting out of turn in grasping the nettle and doing the right thing by making this radical move. After all, the Americans are allowed to fundamentally change their minds about AIDS treatment every five minutes. As with AZT for AIDS cases *in extremis* only (what the FDA licensed it for). Then for people told they’re HIV-positive – when their cell counts are down, even if they’re feeling just fine. As with warning against exposing foetuses to AZT. Then urging it as a good thing. As with the ‘hit early, hit hard’ approach in the mid-nineties – you gobble bracing doses of AZT and other drugs the moment you light up the test. Since AZT turned out to be no good alone. Then the big official U-turn in early 2001, recommending that it’s better to leave the virus alone for as long as possible, before going on the poisonous drugs, so that the patient can live longer. These are the experts, kids.

Although we are still to receive any formal acknowledgement from Council of any of our correspondence, we have learned that individual members have been telephoning Dr Tshabalala-Msimang, telling her that they were ‘amazed’ by the ‘detailed research’ in our preceding letters, and that they had been ‘unaware’ of it. It is obvious that Council has been equally unaware of most, if not all, of the research findings reported in this memorandum. But it certainly knows of them now.

We also know from a confidential disclosure made by one of Council’s members that it is running scared of being sued by the TAC – a not unjustified apprehension, to be fair, in view of the resolution the TAC passed in August 2002 to sue if Council disturbs its victory over the government in the courts, and the fact that the South African judiciary, in
its loftiest reaches, holds the TAC in such high esteem. Why it even enjoined the government to hold hands with it in the battle against AIDS. Because gee we must all fight this together.

But the question we think everyone needs to start asking is: for how much longer are our new democracy, our people and Council going to be held hostage to the pharmaceutical cartel by a neurotic, clinically depressed, scientifically illiterate, American-financed drug industry pimp, posing as a human rights crusader against our liberation movement – appropriately qualified for his controlled, loyal opposition role in the drug business (hence the active assistance of the US Consulate General in Cape Town in getting him funding) with the experience he derived from his work as male prostitute, and a Standard Six. (It should be conceded, though, that the Treatment Action Campaign’s foreign millions are generously shared: unemployed black people from the peri-urban ghettos called out to dance on demand for the cameras get a free summer tee-shirt and R100 (‘for transport and refreshments’).)

As far as deregistering nevirapine for perinatal use is concerned – what we started out asking about, and now long overdue – we don’t think you need lose much sleep over the prospect of being over-ruled and reversed if attacked in the courts by this dreadful person, in the light of a new paper in the pipe, **Low efficacy of nevirapine (HIVNET012) in preventing perinatal HIV-1 transmission in a real-life situation**, by Quaghebeur et al, still in press for publication in *AIDS* 2004 Sep 3;18:1854-1856 but posted online by Pubmed already.

The researchers found that when ‘in a real-life situation in Kenya’ they tried the HIVNET 012 regimen (a hit of nevirapine each for mother and child), it was an unmitigated flop: ‘The perinatal HIV-1 transmission rate at 14 weeks was 18.1%, similar to the 21.7% before the intervention. These data call for further evaluation of the simple nevirapine regimen in field conditions, and underline the need for alternative strategies.’ Game over, so to say.

The authors lamented that ‘despite the lack of validated efficacy data outside research settings’ doctors everywhere went dilly for this ludicrous medical gimmick – just as our clever judges did in prescribing nevirapine for having women and their newborn babies in South Africa, one of whom found the good they were all doing so terribly moving that he burst into tears afterwards. (Told in *The trouble with nevirapine* on the CD we sent you, but also archived at [www.tig.org.za](http://www.tig.org.za).)

And as for retracting your recommendations over AZT use in pregnancy, and then doing whatever it takes, either by way of deregistration, or the issue of a special urgent alert like the FDA and EMEA do from time to
time, to ensure pregnant women and babies don’t come anywhere near this poison, we can’t see that in litigation launched by the TAC a judge with any brains will interfere with your moves after he’s seen the dope contained in this memorandum.

In conclusion might we raise what could seem a rather tangential point? Actually it goes right to the heart of things.

In 1794, writing from a prison cell in Paris for speaking too plainly, the English radical Thomas Paine persisted irrepressibly in *The Age of Reason*:

> As the object of the Church, as is the case in all national establishments of Churches, was the power and the revenue, and terror the means it used, it is consistent to suppose that the most miraculous and wonderful things they had collected stood the best chance of being voted. ... The resurrection and ascension, supposing them to have taken place, admitted of public and ocular demonstration, like that of the ascension of a balloon, or the sun at noonday, to all Jerusalem at least. A thing which everybody is required to believe requires that the proof and evidence of it should be equal to all, and universal. ... Instead of this a small number of persons, not more than eight or nine, are introduced as proxies for the whole world, to say they saw it, and all the rest of the world are called upon to believe it.

So taking Tom Paine’s cue, if it isn’t too impertinent of us to ask: could we also be shown this virus, about which such a fuss is made, on which so much public money is spent, and high-mindedly fighting which, to the great benefit of the pharmaceutical business, so many South African children, mostly black, mostly poor, are in jeopardy of being really messed up, even killed?

At the second meeting of the International AIDS Advisory Panel in Johannesburg in July 2000, this writer was personally witness to a solemn pact clinched, on behalf of the believers, by Professor Barry Shoub, Director of the National Institute for Communicable Diseases, and Professor William Makgoba, then Director of the MRC, and now VC of the University of KwaZulu-Natal.

With his very own eyes this writer saw them pledging to conduct an experiment in which they’d have a go at isolating this terrifying virus in the standard, accepted manner (no short-cuts) from the blood of a person declared infected because his blood had lit up one of these antibody tests used to tell hundreds of South Africans daily, to their great dismay, that they’ve got the virus in them. But we’re all still waiting, because as the gents concerned have shown, they’re not good for their promises; and like
bankrupt hucksters they just duck and dive and make all sorts of excuses whenever reminded.

Could Council maybe give them a friendly call, and ask them what’s holding up the show? It could explain, very properly, that it needs to know, because the continued registration of a whole lot of extremely poisonous big-ticket drugs is on the line. And could you let us know whether it’s because they quietly fret that if the experiment is carried out as agreed they could just come up empty-handed?

It’s a simple request we pose; and if indeed no virus is found – just a few biologically ambiguous traces – it could save the public purse an awful lot of waste, money that could then be much better spent, and spare many people, big and small, but mostly black, mostly poor, unnecessary poisoning and unnecessary suffering. But then again, we reckon that this might be the very impediment, for if no virus is found, and regular folk discover that they’ve all been taken for one hell of a ride, it will be the end of the money for the experts, and guys like Messrs Shoub and Makgoba might have to exchange their white vestments for blue overalls and go out looking for new jobs on the railways. With everyone laughing.

We do appreciate that our wonder about ‘HIV’ sounds rather off-the-wall. Just as it would have been to question the experts a couple of centuries ago with their doctorates in divinity, devilry and demonology, who were telling us that the Devil was corrupting the realm, and that he did so by way of obsession (possession) or by affording ungodly people with maleficient, preternatural powers; whose learned tomes on the subject filled library shelves at the University of Cambridge; and whose evidence in court got the accused (invariably from the working classes) hanged and burned in their umpteen thousands – in England, right up to 1736. (Lynching of accused witches continued in rural parts for well over a century.)

They claimed to know the certain tests: the hidden mole in the armpit, black cats, failure to sink when swum in ponds – dropped in to see, with left thumb tied to right big toe and vice versa – even introspective loneliness among the old, and insufferable insolence among the young. Since hey they were the experts. And some professional witchfinders, like the renowned Mathew Hopkins Esquire, whose evidence saw many people off, went about making a real good living out of it. As luminaries in the AIDS oligarchy do today.

But as you might have understood after reading that all-important Appendix XI to Mother to child transmission of HIV and its prevention with AZT and nevirapine, namely, A critical examination of the evidence for the existence of HIV, our request is maybe not so foolish after all. (If
you found the detail and all those two hundred odd references a taxing read, there’s a simplified version in press for imminent publication in the journal *Medical Hypotheses*. Email us for a preview if you can’t wait.

This is our final friendly request for a formal response from you on the pressing issues we have raised in our correspondence to date. We know you are listening. And you know everyone’s watching. We appreciate that you are sweating in fear of being attacked by the TAC. After all, they do have fans in high places – noisy some of them too, hectoring like a fishwife all the time. We don’t mean to rush you unreasonably. We know that many of the matters raised in this letter will be new: nobody has critiqued the Barret study before, for instance, or lined up all the very latest foetal toxicity studies to demonstrate just how truly crazy it is to give AZT and 3TC and nevirapine to pregnant women and their babies.

Unless, maybe, with South Africa leading the world as its most important and influential new democracy in what our President has rightly called the African Century, thereby threatening the balance of power set by the good ol’ boys, and with anywhere between a quarter and a half of all black women said (by AIDS doctors) to be infected with HIV, there’s some sort of long-term geo-political agenda in play. With AZT lobbed into the country to really take care of things.

We’d like an indication please: how long does Council anticipate it needs to consider all this stuff and make up its mind? We expect an answer to this question in ten working days from date of delivery of this memorandum, calculated from the hour. This business isn’t something we can all dilly-dally over any longer, who’ll disagree?

Yours faithfully

ADV ANTHONY BRINK
CONVENER AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP

Cc: The South African Government, all Provincial Health MECs, media and other interested parties.
Annexure ‘A’


At age 4·5 months, the first patient presented with visual impairment. Cerebral nuclear magnetic resonance imaging showed initially (at age 5·0 months) demyelinating lesions of the brainstem that became more severe and secondarily associated (at 11·0 months) with sustentorial lesions. From age 4·5 months to 11·0 months, the growth was abnormal and associated with vomiting. There were no important hepatic, pancreatic muscle enzyme, or haematological abnormalities, but blood and cerebrospinal fluid lactate concentrations were high (2·5 mmol/L [normal <1·5 mmol/L] and 4·5 mmol/L [<2·0 mmol/L], respectively). The child died aged 13 months because of respiratory and cardiac-rhythm disorders. The symptoms were compatible with Leigh’s syndrome and mitochondrial investigations were done at age 12 months.

The second patient, from age 4 months until death at 11 months, had refractory epilepsy and deterioration of cognitive and psychomotor abilities. Cerebral imaging showed diffuse demyelinating lesions associated with massive cortical necrosis (figure). There were no substantial biological abnormalities for liver, pancreas, muscle, or haematological markers. The blood lactate concentration was high (2·5 mmol/L) but cerebrospinal fluid lactate was normal. Several disorders were excluded because of normal results from the following diagnostic procedures: organic-acid chromatography (urine), aminoacid chromatography (serum, urine, cerebrospinal fluid), serum cholesterol, triglycerides, vitamins A and E, pyruvate dehydrogenase activity in lymphocytes, fatty-acid oxidation and biotinidase activities (lymphocytes), very long-chain fatty acids (serum), lysosomal enzymes (galactosidase, galactosylerceramidase, arylsulfatase A, mannosidase, GM1 and GM ganglioside), copper and ceruloplasmin (serum), and oligosaccharide excretion (urine). These symptoms were consistent with ALPERS syndrome, and led to mitochondrial investigations between ages 5 months and 7 months.

At age 8 months, during a febrile episode, patient three had a seizure and was thought to be hypotonic. At age 15 months, the child showed symptoms of hypokinetic hypertrophic cardiomyopathy. Blood hepatic and pancreatic enzyme concentrations were normal but the child had neutropenia neutrophils 0·931 09/L [normal > 1·531 09/L], high concentrations of muscle creatine phosphokinase in blood (350 IU/L
[<250 IU/L]), and persistently high blood lactate concentrations (4mmol/L), although cerebrospinal lactate was normal. Endomyocardiac biopsy showed intracytoplasmic vacuolisation in myocytes, but without inflammation. The cardiomyopathy progressively improved and symptoms of peripheral myopathy were seen at age 2·5 years. At age 4·0 years, the child’s cardiac function was normal, but moderate muscular deficit persisted; lactate and muscle creatine phosphokinase concentrations in blood remained high. Electreoretinography showed macular and peripheral abnormalities. Cerebral nuclear magnetic resonance imaging was normal.

In the fourth patient, early development was normal. Between ages 14 months and 27 months, the child had four episodes of febrile seizures. Neurological assessment at age 27 months showed mild spastic diplegia. Haematological and biochemical findings, including lactate concentrations in blood and cerebrospinal fluid, were normal. Cerebral nuclear magnetic resonance imaging showed moderate hypersignal of the white matter in T2-weighted images, with no evidence of necrosis (figure).

From age 7 months until 15 months, patient five had repeated seizures. Cognitive development and neurological assessments between episodes were normal until age 15 months. The child developed status epilepticus for 4 h, which led to severe neurological dysfunction with cortical blindness and spastic tetraparesis. Biological tests at 15 months showed only high blood hepatic enzyme concentrations (aspartate and alanine aminotransferases 200 IU/L [<40 IU/L]), which progressively returned to normal. Blood and cerebrospinal fluid lactate concentrations were measured only at the time of mitochondrial assessment and were not retrospectively available. Nuclear magnetic resonance imaging at age 16 months showed large necrotic lesions of the white matter and cortical grey matter. At age 3·5 years the child had severe sequelae and microcephaly.

Patient six was symptom-free until age 14 months, but persistent biochemical abnormalities were seen on standard follow-up of the epidemiological survey (which included lactate assays). The child had had high concentrations of blood lactate (4 mmol/L), hepatic aspartate aminotransferase (50 IU/L), and pancreatic lipase (200 IU/L [<150 IU/L]) since birth that persisted until age 14 months. Cerebrospinal fluid lactate was normal. These biological abnormalities led to specific mitochondrial investigation, including cerebral nuclear magnetic resonance imaging that showed delayed myelinisation, which is difficult to interpret at that age.
Patient seven was symptom-free until age 4 months, at which time he became hypotonic with apnoea. The child regained normal breathing and consciousness after resuscitation, with no apparent sequelae. There were no biological abnormalities during routine biological follow-up, but blood lactate concentrations (routinely assayed in this institution) were continuously high (>4 mmol/L) from the first test at 4 weeks to 7 months. Cerebral nuclear magnetic resonance imaging was normal. Near-miss syndromes and lactataemia justified mitochondrial investigations.

The eighth child was symptom-free. Persistent hepatic and pancreatic abnormalities (alanine aminotransferase 80 IU/L and lipase 180 IU/L) were seen from birth in the routine prospective biological follow-up. Blood lactate concentrations that were systematically added to the normal screening in the institution were normal, as were cerebrospinal fluid concentrations. At age 20 months, biological abnormalities persisted unchanged; a specific mitochondrial investigation was therefore done, including electroretinography, which was abnormal, and cerebral nuclear magnetic resonance imaging that showed abnormalities of the periventricular white matter.

No child was infected with HIV-1, and all were HIV-1 seronegative at age 15 months, or at death before this age for patients one and two. For all children, repeated tests for HIV-1 by PCR and by culture were negative.

Annexure ‘B’

Debating AZT: Mbeki and the AIDS drug controversy

Anthony Brink

Paragraphs 10-13

[10] In his answer to my essay, Martin admits that AZT destroys bone marrow, but then hedges: HIV “may” be the real culprit. This is a tired old tale rehashed. Mercury and arsenic salts - doctors’ favourites for ages - poisoned the patient, whose death was then blamed on unbalanced humours or germs. That AZT destroys bone marrow is frankly declared by its manufacturer. So let’s not fudge. In 1987 in *Annals of Internal Medicine*, Gill et al reported *Azidothymidine Associated with Bone Marrow Failure in the Acquired Immunodeficiency Syndrome (AIDS)*: “Four patients with [AIDS], and a history of Pneumocystis carinii pneumonia developed severe pancytopenia [marked decrease in all types of blood cells] ... 12 to 17 weeks after the initiation of azidothymidine therapy ... Partial bone marrow recovery was documented within 4 to 5 weeks in three patients, but no marrow recovery has yet occurred in one
patient during the more than 6 months since AZT treatment was discontinued.” In the same year in the New England Journal of Medicine Richman et al reported The Toxicity of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex: “Anemia ... developed in 24% of AZT recipients and 4% of placebo recipients (P<0.001). 21% of AZT recipients and 4% of placebo recipients required multiple red-cell transfusions (P<0.001). Neutropenia (<500 cells per cubic millimeter) occurred in 16% of AZT recipients, as compared with 2% of placebo recipients (P<0.001).” The next year, Walker et al followed up in Annals of Internal Medicine reporting Anemia and erythropoiesis in patients with the acquired immunodeficiency syndrome (AIDS) and Kaposi sarcoma treated with zidovudine: “In the current study, transfusion-dependent anemia occurred in 6 of 15 patients with AIDS and Kaposi sarcoma who were receiving zidovudine therapy. All 6 affected patients required their first blood transfusion between 3 and 9 weeks after starting zidovudine therapy, and each required 4 to 14 units of packed erythrocytes to maintain a hemoglobin level above 100 g/L over a 12-week study.” Consistent with this, Costello reported in the same year, in the Journal of Clinical Pathology that, “Blood transfusion is often necessary in patients with AIDS, especially in those receiving AZT, a drug which produces severe anaemia in a proportion of recipients. Forty nine (36%) of 138 patients treated with AZT required blood transfusion at least once.” For AIDS doctors slow to the point, Harrison’s Principles of Internal Medicine spells it out: “[AZT], used for treating [HIV], often causes severe megaloblastic anemia ... caused by impaired DNA synthesis.” Even in the modern age where AZT dosing levels are now hugely reduced, in 1998, in the New England Journal of Medicine, Hymes et al investigated and reported The Effect of Azidothymidine on HIV-related Thrombocytopenia, and found again: “The hematocrit [red blood cell count] decreased in the same patients ... .with three of eight patients requiring red-cell transfusion by the fourth week of treatment.” So did Mocroft et al in their paper in AIDS in 1999: Anaemia is an independent predictive marker for clinical prognosis of HIV-infected patients from across Europe: “We found that 78.2% of the [HIV-infected] patients with mild or severe anaemia at baseline had received zidovudine”.

[11] In their 1988 paper in the British Journal of Haematology, entitled, 3’-Azido-3’-deoxythymidine inhibits proliferation in vitro of human haematopoietic progenitor cells, Dainiak et al reported their investigation of “the mechanism by which cytopenias develop [i.e. cell depletion, which is] ... a serious, dose limiting toxicity of AZT therapy ...” Observing that “Anaemia [during AZT therapy] appears to be due to bone marrow suppression [and] nearly one half of patients treated with AZT for
[HIV]-associated disease develop transfusion-dependent anaemia due to bone marrow depression”, they concluded from their study that “AZT is a potent inhibitor of haematopoiesis in vitro, and that erythroid progenitors are particularly sensitive to its action. These results may explain the marrow hypoplasia that occurs during AZT administration in vivo.”

[12] AZT reaches and can destroy foetal bone marrow too. In the May 1998 issue of the Pediatric Infectious Diseases Journal, Watson et al at the University of Rochester Medical Center in New York reported the case of an HIV-negative baby born to a positive mother who had been treated with a HAART cocktail of AZT, 3TC and a protease inhibitor, suffering “high output congestive heart failure secondary to profound anemia.” The paediatricians excluded “infection, nutritional deficiencies, congenital leukemia and congenital red blood cell aplasia in the child” and considered the “cause of the life-threatening anemia in our infant ... to be in utero erythroid marrow suppression by one or more of the antiretroviral agents administered to the mother.”

[13] Martin alleges that “toxicity in most cases is reversible.” This optimistic jive was flatly contradicted by Mir and Costello just a year after AZT was approved. They reported their concern in the Lancet in 1988 that “bone marrow changes in patients on zidovudine seem not to be readily reversed when the drug is withdrawn. These findings have serious implications for the use of zidovudine in HIV positive but symptom-free individuals.”
THE REGISTRAR: MS PRECIOUS MATSOSO  
MEDICINES CONTROL COUNCIL  
2nd Floor, Hallmark Building  
Cnr Andries and Vermeulen Streets  
Pretoria  

Dear Ms Matsoso

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

In view of Council’s failure to respond to any of our correspondence in the above two matters, we are proceeding with the preparation of a complaint to the Public Protector, preliminary to taking Council’s dereliction of its statutorily mandated responsibilities to the South African public on judicial review, if needs be.

Subsequent to dispatching our last letter to you in the above matter, we located a copy of the finalised version of the draft Antiretroviral drugs and the prevention of mother-to-child transmission of HIV infection in resource-constrained settings Recommendations for use 2004 Revision (the ‘WHO Recommendations’), which we critiqued in our second, fifth and sixth letters, now entitled ANTIRETROVIRAL DRUGS FOR TREATING PREGNANT WOMEN AND PREVENTING HIV INFECTION IN INFANTS’ GUIDELINES ON CARE, TREATMENT AND SUPPORT FOR WOMEN LIVING WITH HIV/AIDS AND THEIR CHILDREN IN RESOURCE-CONSTRAINED SETTINGS (hereinafter referred to as ‘the WHO Guidelines’).

The finalised WHO Guidelines are undated, but according to the WHO’s website were published on 14 July 2004 – that is, twelve days after Council’s meeting at which it decided to disavow nevirapine for solo use to prevent mother to child transmission of HIV in favour of combining it with nucleoside analogue drugs such as AZT.

It is revealed on the ‘Acknowledgements’ page of the WHO Guidelines that the anonymously produced preceding draft WHO Recommendations
were written by long-time collaborators Francois Dabis of the *Institut de Santé Publique, Épidémiologie et Développement (ISPED) Université Victor Segalen Bordeaux 2* in France, and Marie-Louis Newell of the Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health in London, UK.

Both Dabis and Newell are leading members of the ‘IAS Ghent Group’ – more fully named ‘The Ghent IAS Working Group on HIV in Women and Children’.

‘IAS’ is the acronym of the International AIDS Society.

The ‘Acknowledgements’ page of the WHO Guidelines records that a meeting took place ‘in Geneva, Switzerland on 5-6 February 2004 convened by the WHO to review the draft recommendations and [make] suggestions on its revision’, and that South Africa’s James McIntyre attended it.

It is apparent upon a perusal of the finalised WHO Guidelines, however, that there is no substantial difference between their contents and those of the draft WHO Recommendations, and that the former are essentially the latter reframed. It is plain therefore that nothing new or original of any substance was contributed by any of the consultants invited to ‘review the draft recommendations and [make] suggestions on its revision’, and that Dabis and Newell must accordingly be credited as the principal authors of the finalized WHO Guidelines and of the treatment prescriptions they proffer.

Although winsomely sub-titled *GUIDELINES ON CARE, TREATMENT AND SUPPORT FOR WOMEN LIVING WITH HIV/AIDS AND THEIR CHILDREN IN RESOURCE-CONSTRAINED SETTINGS*, the WHO Guidelines have nothing to say about care and support in the ordinary sense of these expressions and everything to say about what antiretroviral drugs pregnant women and their babies should be put on as soon as possible.

This is because to Dabis and Newell, and AIDS doctors in general, ‘care’ has acquired the peculiar meaning conceived by the marketing arm of the pharmaceutical industry, namely, the administration of antiretroviral drugs: at a satellite meeting held on 12 July 2004 at the Bangkok AIDS Conference to discuss their about-to-be-released WHO Guidelines, they claimed them to be ‘expert consensus documents ... developed over the past six months in partnership with the Ghent IAS Group using available evidence and in the context of increasing access to care of women and children’. By this they mean in the context of the WHO’s ‘Treat 3 million
by 2005’ with antiretroviral drugs programme, whose motto is emblazoned on the cover of their WHO Guidelines.

This programme dovetails with the long-term marketing strategy of nevirapine manufacturer Boehringer Ingelheim: its summer 2004 edition of *VIRAMUNE-Access Update*, puffed by a front-page colour photograph of a pair of happy natives, explains the company’s business development plan:

Boehringer Ingelheim is in its fifth year since it announced the VIRAMUNE [nevirapine] Donation Programme, one of its contributions to the alleviation of HIV/AIDS around the world. Since then, VIRAMUNE has been provided free of charge for the Prevention of Mother to Child Transmission of HIV. Boehringer Ingelheim and WHO recognise the potential for PMTCT sites to serve as natural entry points for providing access to chronic treatment within the “3X5” strategy. This means that the healthcare infrastructure that has been built up through PMTCT programmes will be leveraged to eventually lead to greater access to chronic treatment in these communities.

Boehringer Ingelheim has even established a caring charity:

The Boehringer Ingelheim Cares Foundation, Inc. is an independent, not-for-profit tax-exempt organization established in 2001 by the Boehringer Ingelheim Corporation in Ridgefield, CT [Connecticut, US]. The Foundation’s mission is to improve lives through innovative philanthropic contributions and donations of healthcare products and resources.

None of the literature concerning the foetal and neonatal toxicity of antiretroviral drugs that was published concurrently with or subsequent to the release of the draft WHO Recommendations on 7 January 2004, which we canvassed in our last letter to Council, was mentioned in the final WHO Guidelines – much less were its grave implications for the use of antiretroviral drugs in pregnancy discussed.

It is evident therefore that neither Dabis nor Newell checked whether any relevant new toxicity research had been reported between the date that their draft WHO Recommendations were released and the publication of the finalised WHO Guidelines more than six months later.

And from their failure to draw these authors’ attention to this latest reported research at the Geneva meeting, it is equally plain that none of the people hired to discuss and comment on the draft WHO Recommendations – South Africa’s James McIntyre included – had
bothered themselves with keeping abreast of the current toxicity literature either.

Dabis and Newell’s new WHO Guidelines are accordingly situated solidly within the currently hegemonic chemothterapeutic approach to AIDS, sold to clinicians and academics by the pharmaceutical cartel, a medical paradigm to which the International AIDS Society is entirely beholden – as is plain from the prominent advertisement of the industry’s AIDS drugs on the website of the IAS journal *AIDS*, hard copies of which are thick with AIDS drug advertisements.

Although the IAS styles itself altruistically as ‘Scientists and Healthcare Workers Committed to HIV/AIDS’, in reality what the IAS is ‘committed to’ is the movement of pharmaceutical industry merchandise. A leading member of Dabis and Newell’s IAS Ghent Group, and a prominent consultant on their WHO Guidelines, is Joep Lange, just-retired president of the IAS, and current chairman of PharmAccess International, an AIDS drug lobby group, whose name unambiguously proclaims its mission in developing countries on behalf of the drug industry cartel.

With the cartel breathing heavily behind them, there’s naturally not a mention in the WHO Guidelines of caring in the form of nutritional support for ‘children in resource-constrained settings’, notwithstanding plenty of reports like Beisel’s in October 1996 in the *Journal of Nutrition* (126(10 Suppl):2611S-2615S), *Nutrition in pediatric HIV infection: setting the research agenda* *Nutrition and immune function: overview:*

Malnutrition can have adverse, even devastating effects on the antigen-specific arms of the immune system and on generalized host defensive mechanisms. ... Immunological dysfunctions associated with malnutrition have been termed Nutritionally Acquired Immune Deficiency Syndromes (NAIDS). Infants and small children are at great risk because they possess only immature, inexperienced immune systems and very small protein reserves. The combination of NAIDS and common childhood infections is the leading cause of human mortality. NAIDS can generally be corrected by appropriate nutritional rehabilitation, but from a viewpoint highly important to this Workshop, AIDS and NAIDS are intensely synergistic. AIDS-induced malnutrition can lead to the secondary development of NAIDS, with its much broader array of additional immunological dysfunctions. The complex and far reaching insults to the immune system caused by NAIDS, and the synergistic combination of NAIDS and AIDS, thereby hasten the demise of many victims of AIDS. Aggressive nutritional support for children with HIV infections could delay, or
lessen, the development of NAIDS and avoidance of NAIDS would improve both quality and length of life.

Dabis and Newell’s endearing reference in their WHO Guidelines’s subtitle to ‘women ... and their children in resource-constrained settings’ is European code for Africans: ‘In 2003 an estimated 700 000 children were newly infected with HIV, about 90% of these infections occurred in sub-Saharan Africa.’ AIDS drug experiments on pregnant African women and their babies are mentioned throughout the WHO Guidelines. In reference to a clinical trial conducted in Thailand, Dabis and Newell mark the principal intended territory for the application of their WHO Guidelines: ‘Although these trial data are reassuring, it is not known whether ZDV from 28 weeks in Africa will result in serious anaemia in programmes where anaemia is common and women are not screened.’ And in a recent statement by Newell, discussed below, she urges that ‘we cannot ignore the AIDS epidemic taking place today in Africa today’ and that ‘It is our duty to disseminate the results of this study, and other research taking place across Europe.’

Dabis and Newell’s claim that their WHO Guidelines represent the ‘expert consensus’ springs from the simple expedient of having consulted very narrowly – specifically, only those clinicians known to share their medical thinking.

In the all-important matter of drug safety, Dabis and Newell failed to solicit the advice of any scientist or clinician who has contributed to the foetal toxicity literature. None of the participants in the ‘Technical Consultation on Antiretroviral Drugs and the Prevention of Mother-To-Child Transmission of HIV Infection in Resource-limited Settings’ – the meeting mentioned above – ‘to review the draft recommendations and for making comments and suggestions on its revision’, nor any other persons listed who were approached for ‘comment ... on [Dabis and Newell’s] first draft’, nor any of the ‘WHO staff [who] contributed to writing these guidelines’ have any specific expertise in the subject of toxic pharmacology, both demonstrated in numerous clinical and experimental studies, and potential, having regard to all that is known about the toxicity of AIDS drugs – nucleoside analogues in particular, described by Brinkman et al. in September 1999 in *Lancet* (354 (9184):1112-5) as ‘much more toxic than we considered previously’.

On the contrary: another of Dabis and Newell’s senior consultants was UNAIDS’s HIV/AIDS Programme chief Joseph Perriens (mentioned in our second letter), famously on record in the *New York Times* describing AZT as ‘slightly more toxic than an aspirin’. (Like Cape Town University Medical School Dean Professor Nicky Padayachee, a loyal AIDS drug
pusher too, Perriens is in the pay of the pharmaceutical drug industry and the American government. Both Perriens and Padayachee are members of another AIDS drug promoting outfit, ECI (Enhancing Care Initiative), ‘a multidisciplinary, multinational program that aims to enhance the care of people living with HIV/AIDS in resource scarce countries’, co-funded by AIDS drug manufacturer Merck and the US Department of Health and Human Services.)

Another consultant who approved Dabis and Newell’s draft was the FDA’s thoughtful Ellen Cooper, whom we quoted in our last letter:

We don’t know what the long-term effects of AZT use during pregnancy might be, but so far we have seen virtually no adverse effects in the short term. ... Not one single tumor. Not one. ... I mean [the children] have cancers, lymphomas, and other problems like that ... but there’s no reason to link those cancers to AZT.

Local consultant James McIntyre is a GlaxoSmithKline asset, who sang AZT’s praises (‘the muthi’, he calls it) from the pulpit of the company temple in the centre of the exhibition hall at the 13th International AIDS Conference in Durban in July 2000. Tweedledum to this Tweedledee is his colleague at the Paediatric AIDS Unit at Chris Hani-Baragwanath Hospital, cartel bimbo Glenda Gray, who responded to President Mbeki and Dr Tshabalala-Msimang’s stated concerns about the toxicity of AZT in 1999 by pouting in the Washington Post on 16 May 2000: ‘If they’re not going to provide us with AZT then the best thing that the government can do is to ask us to strangle them all at birth.’

This was the luminous quality of the intelligence that Dabis and Newell had at their disposal during the review of their draft WHO Recommendations in Geneva.

Concerning the safety of nevirapine taken during pregnancy, Dabis, Newell and their consultants seem to have short memories. The transplacental cytotoxicity of nevirapine was established in murine studies even before the drug was provisionally licensed in the US in 1996, and thereafter elsewhere in the world, with Boehringer Ingelheim cautioning in its license application to the FDA: ‘In rats ... a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.’

Yet the lesson of thalidomide is that humans are much more susceptible to injury by transplacental toxins than animals. In pregnancy safety studies duly conducted by the manufacturer, rodent foetuses experimentally exposed to thalidomide were not born deformed as humans later were (see photograph annexed), which is how and why the
directors of thalidomide manufacturer Chemie Grünenthal got off the hook at their prosecution in Aachen, West Germany in the sixties.

And when on 5 January 2001 the US CDC issued a special contraindication advisory against even four-week use of nevirapine by health professionals following needlestick injuries, the Health Systems Trust published a reassuring note a week later in HealthLink Bulletin that:

The South African pilot studies to reduce mother-to-child transmission of HIV through the administration of nevirapine will not be delayed by recent reports of drug toxicity. However the women participating in the program will be closely monitored, according to recent press reports. The CDC in the US recently issued a warning on the toxic side effects of nevirapine when administered over several weeks. ... These included severe liver damage, when used to treat health care workers accidentally exposed to HIV by needle sticks. However, vertical transmission prevention requires only one dose of the drug. ... The reports on the toxicity of Nevirapine will have no impact on the Democratic Alliance’s proposal to provide the medicine free to HIV-positive pregnant women in the party’s controlled municipalities. Party spokesman Sandy Kalyan said reports of Nevirapine being potentially harmful concerned multiple doses of the drug. ... The South African Medicines Control Council last year registered nevirapine and approved its use for trials after UNAIDS and WHO endorsed the drug as a safe treatment for one-off use in the recommended dosage, saying the benefits outweighed the potential adverse effects. [Our emphasis.]

In embracing Dabis and Newell’s WHO Guidelines, Council has abandoned its former caution, having regard to the CDC’s warning three years ago that ‘healthy persons taking abbreviated 4-week NVP regimens for PEP are at risk for serious adverse events’ such as ‘Severe, life-threatening, and fatal cases of hepatotoxicity and skin reactions. ... The median onset of these symptoms was 14 days after beginning NVP for PEP (range: 3 – 36 days).’

Irrespective of this, the WHO Guidelines propose that African women endure the acute, severe toxicity of nevirapine throughout their pregnancies, with their unborn babies exposed transplacentally all the while, no matter that rodent studies conducted by Boehringer Ingelheim found ‘significant decrease in fetal weight’ resulting from exposure in utero.

Even single-dose nevirapine treatment after birth has again been shown recently to be very toxic for a high proportion of treated babies: a study by Taha et al., Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled
trial, was published in *Journal of the American Medical Association* (292(2):202-9) on the same day as the WHO Guidelines – which mentioned the study (citation 33) as a paper still in press that ‘showed no benefit of adding ZDV for one week to neonatal single-dose NVP when the mother had received intrapartum NVP’.

What Dabis and Newell neglected to mention in their WHO Guidelines is that the study also found an incidence of ‘Grades 3 and 4 adverse events’ at a rate of ‘4.9% ... and 5.4% ... in infants receiving NVP only and NVP plus ZDV, respectively’. That is, one in twenty African babies suffered serious toxic reactions to the drugs. But then the AIDS doctors who reported the study weren’t troubled by this either, noting simply: ‘The safety of the regimen containing neonatal ZDV was similar to that of a standard NVP regimen.’

Dabis and Newell’s failure to consult broadly goes some way to explaining why they gave the ‘available evidence’ concerning the foetal toxicity of antiretroviral drugs such short shrift in their draft WHO Recommendations and finalised WHO Guidelines.

A further reason accounting for the dangerously inadequate two-page treatment they accorded the all important issue of maternal, foetal and neonatal safety in their fifty page WHO Guidelines is the fact that both of them are epidemiologists, a medical speciality concerned with tracking the occurrence of disease in given populations – a distant remove from clinical medicine, molecular biology, molecular pharmacology, medical toxicology and pathology. (This also explains their shared ignorance and their fundamental misapprehensions as to the (very limited, non-diagnostic) clinical meanings of antibody and genetic ‘HIV’ test results, on the fallacious basis of which they have erected their careers in purportedly preventing African mothers from infecting their babies with HIV.)

In writing their WHO Guidelines, notwithstanding their professional interest in disease incidence, neither Dabis nor Newell had any regard to the appearance of clinical disease among the babies in the studies they cited; instead their preoccupation was with laboratory testing outcomes, on the corrupt assumptions that HIV-antibody-positive, or a certain ‘viral load’ measure, equates with disease (HIV-infected), and the inexorable development of disease (AIDS). Which is flat wrong on all scores. We’ve dealt with the tests before; in March 2002 Morgan et al. reported in *AIDS* (16:597-603) that untreated ‘HIV infected’ Ugandans are surviving ‘considerably longer than has been expected’. Just as all the predictions once made for supposedly deadly Hepatitis C Virus have likewise flopped.
Like all AIDS doctors propounding the use of the pharmaceutical industry’s wares in pregnancy, Dabis, Newell and their consultants also appear to be unaware of the European Collaborative Study’s finding reported in *Lancet* in November 1988 (2(8619):1039-43) that without any drug intervention most babies spontaneously sero-revert to HIV-negative in any event. Which is to say – proceeding from AIDS doctors’ universal fallacy that HIV-positive means HIV-infected – that most HIV-positive babies spontaneously cure themselves of HIV infection without the intervention of AIDS doctors and their pills.

And as we pointed out in our last letter, several studies in which the clinical effect of treating pregnant women with AZT has been investigated have found that babies exposed to the drug in utero suffer substantially higher death, serious disease and other health impairments than unexposed babies. And the HIVNET 012 single dose nevirapine regimen has been found to have no clinical health benefit when the mortality rate of treated children is compared with that of untreated ones.

Despite the fact that the HIVNET 012 study was a hopeless mess (and for some remarkable news, see the post script hereto), Dabis and Newell persist in citing it in their WHO Guidelines in support of the single-dose perinatal nevirapine regimen tried in the study (citations 7 and 8).

Boehringer Ingelheim’s main German website also still pretends that nothing’s remiss:

Viramune® may be used alone as a single oral dose to the mother during labour and a single oral dose to the infant within 24 hours after birth for the prevention of mother-to-child transmission of HIV-1 pregnant women who are not taking antiretroviral therapy at time of labour.

But the company hastens immediately thereafter to make clear that this special drug indication is intended for dun-hued mothers and babies, not fair ones:

Disclaimer:

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Therefore please check the registration details of this/these product(s) locally in order to get up-to-date information.

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The case of thalidomide neuropathy is also instructive concerning the limits to safety conclusions that can be drawn from toxic injury reports. Although well-known as a foetal teratogen, little known is that thalidomide is a potent neurotoxin, which caused many thousands of adult Europeans ingesting the drug to suffer permanent neuropathy at an incidence of about one in five exposures. Yet not a single report of neuropathy among lepers given the drug in the developing world has been published in the medical literature.

The perfect harmony between the commercial aims of the pharmaceutical drug industry, those of Dabis and Newell’s IAS, and those of the WHO, are naturally and inevitably manifest in the WHO Guidelines.

Dabis’s professional commitment to the administration of synthetic pharmaceutical drugs as the perfect solution to what he declaims dramatically in the preface to the WHO Guidelines as ‘the greatest health crisis the world faces today’, to the exclusion of all alternative nutritional and natural treatment modalities, is evident from his discouragement of breastfeeding by HIV-positive mothers in his WHO Guidelines and from other platforms, and his bid (in *Lancet* 1998 Aug 22;352(9128):653-5) to discredit research published by the Harvard School of Public Health that
has shown that vitamin supplementation is effective in reducing mother to child transmission of HIV according to the usual surrogate indices.

Dabis and Newell’s professional bias in favour of the use of antiretroviral drugs during pregnancy and after birth, the blithe manner in which they discount the toxicity literature, where they treat it at all, and their disregard of alternative non-toxic interventions, arise from the following:

Both have long championed the administration of AZT to pregnant women in the developing world, and cite their own research work, its interpretation and the conclusions they draw from it, in support of the recommendations they make in the WHO Guidelines. Indeed, an ardent proponent of AZT use in pregnancy, on which he has built his career and reputation, Dabis cites his own experiments on African mothers and their children in Côte d’Ivoire and Burkina Faso in support of his antiretroviral drug treatment recommendations expressed in the WHO Guidelines no less than five times – citations 11, 16, 23, 24, 38 – more than any other researcher’s.

Dabis’s manifest conflict of interest arising from his own professional investment in the administration of AZT to Africans naturally disqualifies him from (a) giving impartial consideration to ‘the available evidence’ where it militates against the medical treatment he has made his name advocating, i.e., the latest research reports concerning the harm it causes children, (b) from according these findings due weight, and (c) from considering the possibility that the relatively recent (only decade-old) medical practice of exposing mostly non-white unborn and newly born babies to such potent transplacental cytotoxins as AZT, 3TC and nevirapine has been a grave mistake, a terrible wrong turn in contemporary medical practice.

Newell’s professional incompetence in assessing the significance of the latest published evidence that AZT and 3TC have seriously harmful toxicity for unborn and newly born babies, and consequently should never be used during pregnancy and post partum, is revealed by the fact that two months after the French Paediatric HIV Infection Study Group published its final report in August last (the Barret study referred to in our second, fifth and sixth letters) concerning the serious, sometimes fatal, foetal and neonatal toxic effects of AZT or AZT+3TC, she wrote (with Thorne) in Antenatal and neonatal antiretroviral therapy in HIV-infected women and their infants: a review of safety issues, published in the October-December issue of the Polish paediatrics journal Medycyna wieku rozwojowego (7(4 Pt 1):425-36), that
Concerns regarding mitochondrial dysfunction in children with foetal/neonatal exposure to zidovudine have arisen following a report from France of eight uninfected children with mitochondrial dysfunction, of whom two died. However, there is limited additional evidence of clinically evident mitochondrial disease in children exposed to antiretroviral therapy in utero or neonatally, and the absence of any excess mortality in large observational cohort studies of children born to HIV infected women and exposed to antiretroviral drugs is reassuring.

Newell’s reference was to what the French Paediatric HIV Infection Study Group called their ‘Preliminary report’ (the Blanche report) four years earlier. She’d apparently missed its final one (the Barret study) in August.

That only a few children were reported killed by AZT and 3TC in the ‘Preliminary report’ Newell considered ‘reassuring’. That other children were reported gravely neurologically crippled, she evidently thought to be of no account. And passing her by was the obviously defective methodology in other studies that counted drug deaths only and thereby missed further such grave injury cases – as discussed in the Barret study. Even less did it enter Newell’s head that very many more cases of subclinical neurological harm would have gone unrecorded in ‘observational cohort studies’ as coarse as corpse counts.

In this latter regard, we wish to emphasize that it is not only gross and sometimes fatal neurological damage caused by the use of antiretroviral drugs in pregnancy that ought to be of concern to Council, but also subclinical irreversible neurological injury – the sort of damage that would not be immediately apparent upon clinical examination and so would not attract closer attention and investigation, as was the case in the drug-exposed children investigated by French Paediatric HIV Infection Study Group (the Blanche alert, the Barret study), where electrophysiological investigation of every drug-exposed child, including the recording of sensory nerve action potentials (SNAPs), would doubtlessly have detected wide-scale subclinical neuropathy. The French Group researchers’ failure to appreciate this would certainly have led to countless damaged children going unrecorded, since the only children investigated were those who exhibited gross clinical manifestations of drug injury.

Of all human organs, the brain and nervous system is the most sensitive to toxic chemical damage, especially during foetal and neonatal development. Significant permanent chemical harm to the nervous system
may go undetected without specialised testing, and yet will substantially diminish a child’s and later adult’s quality of life.

It’s revealing that in common with Dabis and all other AIDS doctors, Newell also disdains natural childbirth and breastfeeding by African women diagnosed HIV-positive in favour of surgeons’ knives and formula milk. This is despite the absence of any clinical evidence whatsoever that African babies delivered by medically imposed Caesarean section have better clinical health outcomes than babies born naturally. And, as might be expected by any informed person with any common sense, there is equally no clinical evidence whatsoever that babies denied their mothers’ breast milk at the instance of AIDS doctors are healthier than babies fed factory-produced formula milk – whatever the mothers’ ‘HIV status’. But the abstract to Newell’s article in Med Wieku Rozwoj nonetheless commenced brightly:

Specific interventions to prevent mother-to-child transmission (MTCT) include antiretroviral therapy, elective caesarean section and avoidance of breastfeeding. Rates of MTCT below 1-2% are now achievable in developed country settings.

A recent press release by her University College, London – on 14 September 2004 – quoted Newell making the same claim:

HIV infected pregnant women who choose an elective caesarean can reduce by half the risk of infection to their child, while breastfeeding increases the risk of transmission. Although with the application of a number of interventions, the rate of mother-to-child infection has been successfully reduced to 1% in Europe, we cannot ignore the AIDS epidemic taking place today in Africa today. It is our duty to disseminate the results of this study, and other research taking place across Europe.

Ghent IAS Group member Ruth Nduati expressed this perverted medical antipathy – standard among AIDS doctors, yet contrary to reams of literature reporting the benefits of breastfeeding for every aspect of physical and intellectual development and long term health, and the harmful deficiencies of substitute factory-made milk – in her opening address at an IAS meeting on 16 July 2003 to discuss and promote the use of AIDS drugs during pregnancy, in which she alleged that ‘breastfeeding continues to diminish the efficacy of protocols to administer’ AIDS drugs to pregnant women, because, she said, ‘about 44% of the transmission is through breastfeeding’.

(This orthodox medical stupidity is currently being imparted by South African AIDS doctors to African women at antenatal clinics and
hospitals: David Coetzee told the IAS meeting that ‘96 per cent of the women [attending antenatal clinics in the poor shack settlement of Khayelitsha, Cape Town] said they did not breastfeed at all ... in order to prevent transmission to their child’.

Clearly ignorant of the latest published toxicity research canvassed in our sixth letter, and dull to the dire significance of the toxicity reports that she glossed over in her WHO Guidelines, Newell again (in this latter document) shared with us that she found it ‘reassuring’ that

MTCT prophylaxis with short-course ZDV was not associated with short-term clinical or laboratory toxicity among pregnant women in several controlled trials and long-term follow-up. Trials from Thailand suggest that serious anaemia in women receiving ZDV from 28 weeks of pregnancy is rare and no increase in serious haematological toxicity was observed with ZDV started at 36 weeks in trials in Africa. Although these trial data are reassuring, it is not known whether ZDV from 28 weeks in Africa will result in serious anaemia in programmes where anaemia is common and women are not screened.

In other words, although it’s ‘not known whether ZDV from 28 weeks in Africa will result in serious anaemia’ – that is, potentially fatal destruction of infant (and maternal) bone marrow and red blood cells – Dabis and Newell suggest that the drug be prescribed to African women throughout their pregnancies regardless:

Although there are concerns relating to potential effects of ARV drugs on the developing fetus, suspending treatment during the first trimester is generally not recommended. ... For eligible women, ARV treatment should be started as soon as possible during pregnancy. ... ZDV [AZT] should be included in the regimen whenever possible. ... A regimen consisting of ZDV starting from week 28 of pregnancy, single dose NVP and ZDV during labour plus ZDV for one week given to the infant is highly efficacious.

It’s worth mentioning, as a vignette showcasing the quality of thinking expressed in their WHO Guidelines, that Dabis and Newell cite Bardeguez et al. (in Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2003, 32(2): 170–181) noting that ‘HIV-related disease progression does not appear to be altered by receiving ZDV prophylaxis’. That is to say, taking antiretroviral drugs does not make sick pregnant women better, or prevent healthy pregnant women getting sick on the drugs – a finding they elsewhere contradict in their WHO Guidelines: ‘Potent combination treatment has substantial benefits for the woman’s health ...’
This latter claim – right out of a drug industry advertisement – is contradicted by numerous clinical studies, most recently by Reisler et al. in *Journal of Acquired Immune Deficiency Syndromes* (2003 Dec 1;34(4):379-86); and by Brown et al., who presented similar, albeit obfuscated findings at the 15th International AIDS Conference in July 2004 in Bangkok: **Non-AIDS serious adverse events are as important as AIDS events in patients with advanced multi-drug resistant HIV disease.**

Upon an analysis of ‘serious or life-threatening events that are not AIDS defining, AIDS events, and death among patients treated with highly active antiretroviral therapy (HAART) in the setting of 5 large multicenter randomized treatment trials conducted in the United States’ Reisler et al. discovered, as they reported both in their conclusion and in the title to their paper, that **Grade 4 events are as important as AIDS events in the era of HAART**, i.e. that people given ‘potent combination therapy’ have an approximately equal chance of being dangerously poisoned or killed by AIDS drugs as they do of developing AIDS defining diseases. Which, in as many words, GlaxoSmithKline long ago admitted that AIDS drugs can cause in its entry under ‘Retrovir’ (AZT) in the *Physician’s Desk Reference*: ‘... it was often difficult to distinguish adverse events possibly associated with administration of Retrovir from underlying signs of HIV disease or intercurrent illnesses.’ And all of which would lead most ordinary guys to wonder what the point of taking the drugs is, in pregnancy especially.

By their silence as to the critical matter of drug dosing levels, Dabis and Newell imply in their WHO Guidelines that the prophylactic doses of AZT, 3TC and nevirapine combinations given to pregnant African women and their newborn babies should be the same as therapeutic ones – the ones good at causing life-threatening Grade 4 events.

This reading is supported by the US Department of Health and Human Services’s publication *A Guide to the Clinical Care of Women with HIV* (2000), which echoes the US CDC’s still current recommendation in *Morbidity and Mortality Weekly Report* 1998; 47[RR-2] that ‘pregnant women should be treated according to standard guidelines for antiretroviral therapy in adults’. In other words, American AIDS doctors don’t see any need to reduce the usual dose to protect the foetus.

These dose recommendations, however, were made during the ‘hit early, hit hard’ HIV treatment era in full swing, with high-dose, multi-drug combinations being the medical convention, before the reported human toll on AIDS patients – described by AIDS treatment expert Professor Michael Saag of the University of Alabama in *Esquire* on 1 March 1999:
‘They aren’t dying of a traditionally defined AIDS illness. I don’t know what they’re dying of, but they are dying. They’re just wasting and dying.’ – led the US Department of Health and Human Services to renounce this brutal mediaeval treatment orthodoxy in favour of delaying initiation of antiretroviral treatment for as long as possible:

On 5 February 2001 the US National Institutes of Health released their *HIV Treatment Guidelines Updated for Adults and Adolescents* – summed up by US government’s top AIDS don, National Institute of Allergy and Infectious Diseases (NIAID) director Anthony Fauci the day before in the *New York Times*: ‘We are adopting a significantly more conservative recommendation profile’ – the idea being, as the reporter paraphrased him, to allow ‘the virus to remain in the body longer in return for sparing the patient the drug toxicities’.

This official U-turn in AIDS treatment policy, abruptly and somewhat embarrassingly ending AIDS doctors’ ‘hit early, hit hard’ craze, was followed by another officially endorsed reversal: patients put on antiretroviral drugs should be given treatment holidays to ‘reduce toxicity’:

**Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic, and toxicity parameters** by Dybul et al. – including Fauci – was published in December the same year in *Proceedings of the National Academy of Sciences* (98(26):15161-6), reporting that by all conventional surrogate markers patients did no worse from having treatment holidays: a week on, a week off. This paper thus debunked the ‘resistance’ argument with which AIDS doctors had terrorised their suffering patients to ‘adhere’ to their drug prescriptions or die.

Since ‘Adherence to such a regimen may be problematic for certain patients’, i.e. even alternate weeks will be unendurable, the same principal authors (Fauci included again) have recently came up with another idea: **A proof-of-concept study of short-cycle intermittent antiretroviral therapy with a once-daily regimen of didanosine, lamivudine, and efavirenz for the treatment of chronic HIV infection**, published in June this year in the *Journal of Infectious Diseases* (189(11):1974-82), found that it did no harm to reduce drug combination intake to one dose a day.

But paying no heed to these huge, successive retreats from formerly aggressive AIDS treatment convention, Dabis and Newell’s WHO Guidelines offer no such medical mercy for pregnant African women and their babies, and instead move in precisely the opposite direction. Whereas in 1998 UNAIDS, the WHO and UNICEF endorsed short-
course AZT treatment of pregnant women to reduce mother to child transmission of HIV, Dabis and Newell’s current WHO Guidelines urge aggressive triple combinations of AZT, 3TC and nevirapine, administered without respite throughout pregnancy or started after a month into it.

The look of it is that as AIDS drugs are being progressively retired in the north, with the mounting toxicity data threatening to block out the sun (as was the case with mercury and arsenic salts in their dying days in the early 20th century), the pharmaceutical industry is manoeuvring to dump them in the south.

This is what happened after the thalidomide disaster: in 1965, as German prosecutors were preparing the indictment of Chemie Grünenthal’s directors for their criminal prosecution, the company resumed production of the drug to take up the slack in its vast production capacity. Since thalidomide had been invented as a cell-poison in 1953, and had initially been marketed for a couple of years from 1956 onward as an antibiotic for respiratory infections (it was notoriously repackaged as mother’s little helper between 1958 and 1962), Chemie Grünenthal began marketing the drug in the third world as a treatment for out-of-sight lepers. The ‘inevitable result’, according to the Oxford Companion to Medicine is that “thalidomide babies” are once again being born, notably all over South America.

Incredibly, in 1998 the WHO approved this new treatment indication. Four years later the WHO quietly revoked its imprimatur on this diabolical abuse, but without any concessions as to the harm it had caused and the magnitude of the organisation’s failure to the most vulnerable of the developing world’s poor. Thalidomide continues to be manufactured and hawked in South America, where it is still deforming children on that continent today. (Could it be that the absence of any public outrage over this in the West is due to the fact that the deformed children are not white?)

The WHO’s support, until recently, for the use of thalidomide in the developing world, right after it had been banned in the first, presents a vivid illustration of how the WHO has been hijacked by the pharmaceutical cartel and by the faithful clergy it directly and indirectly retains in medical orders worldwide; and it explodes any illusion that the WHO functions as an impartial international body applying the best available science, and beyond the dictates of the cartel’s utterly ruthless commercial programme.

We suggest that the integrity, authority and reliability of the WHO Guidelines should be assessed in the light of the organisation’s colossal
betrayal of the people of the developing world in the recent thalidomide fiasco.

Dabis and Newell make their violent treatment proposals despite a mass of foetal toxicity and multi-drug toxic synergy reports that have been published subsequent to the adoption of the AZT short-course policy in 1998.

Any informed and thoughtful doctor would have been impelled to greater caution by these studies, but instead, for unborn (and newly born) African babies, Dabis and Newell recklessly extend the duration and variety of drug exposure. And without thinking, Council goes along.

The WHO Guidelines effectively codify best clinical practice regarding the prescription of AIDS drugs to HIV-positive women and their babies in the developing world; and after the brief single-dose nevirapine interregnum, they mark the return of AZT with a vengeance.

Having been synthesized as an experimental cell poison in 1961 (see the writer’s essay Inventing AZT posted at www.tig.org.za), AZT was licensed by the FDA in 1987 as an AIDS drug not because it had any demonstrated antiviral activity (it was pertinently noted by the FDA licensing panel that none had been shown – and still hasn’t, as you will have read in Papadopulos-Eleopulos’s et al. mammoth analysis of the molecular pharmacology of the drug that we sent up to you), but because it appeared, on a superficial look at the mortality data in the Phase II AZT trial, to extend lives (but see the writer’s exposé of the trial, Licensing AZT, on the said website).

AZT and 3TC are nucleoside analogues, a class of drug employed in cancer chemotherapy purposely to kill human cells, as discussed in a leading textbook in this subject by Cheson et al, Nucleoside Analogs in Cancer Therapy (Marcel Dekker Inc. New York, 1997).

And don’t go believing GlaxoSmithKline’s lies that AZT is somehow specific for HIV and doesn’t kill human cells like all other nucleoside analogue drugs in its chemical class (‘Competition by zidovudine-TP for HIV reverse transcriptase is approximately 100-fold greater than for cellular DNA polymerase alpha’), because Gill et al. reported great success slaughtering blood cells with AZT in a study reported in June 1995 in the New England Journal of Medicine (332(26):1744-8): Treatment of adult T-cell leukaemia-lymphoma with a combination of interferon alfa and zidovudine. As did Ermine et al. simultaneously in the same journal: Treatment of Adult T-Cell Leukemia-Lymphoma with Zidovudine and Interferon Alfa.

For killing blood cells, AZT’s as good as ever: Aouba et al. have recently published a study consistent with those preceding: **Hemophagocytic syndrome as a presenting sign of transformation of smoldering to acute adult T-cell leukemia/lymphoma: efficacy of anti-retroviral and interferon therapy** in June 2004 in the *American Journal of Hematology* (76(2):187-9). But then the bottle – labelled by Sigma Chemical Company more honestly than GlaxoSmithKline – does say: ‘**Toxic** Toxic to inhalation, in contact with skin and if swallowed. Target organs: Blood Bone marrow ... Wear suitable protective clothing.’

AZT’s not only deadly poisonous to blood cells; it’s been used with great effect to deliberately kill other human tissues too: in January 1999, in the *Journal of the American Academy of Dermatology* (40(1):116-21), Chan et al. reported **A novel chemotherapeutic regimen (interferon alfa, zidovudine, and etretinate) for adult T-cell lymphoma resulting in rapid tumor destruction.**

The dangers of exposing a growing foetus to nucleoside analogues are accordingly well-recognised in cancer chemotherapy.


> It is not advisable to become pregnant or father a child while taking fludarabine [a nucleoside analogue drug] as it may harm the developing foetus. It is important to use effective contraception whilst taking this drug, and for at least a few months afterwards.

Another cancer treatment information service, CancerHelp UK, warns alike concerning the use of the drug. Because it

> stop[s] cells making and repairing DNA ... This drug may have a harmful effect on a baby that is developing in your womb. It is not advisable to become pregnant or father a child if you are having this drug. You should talk about contraception with your doctor before having the treatment.
The American Cancer Society similarly warns under ‘Pregnancy’:

Although pregnancy may be possible during chemotherapy, it is not advisable because some chemotherapy may cause birth defects. Doctors advise women of childbearing age, from the teens through the end of menopause, to use birth control throughout their treatment.

- If a woman is pregnant when her cancer is discovered, it may be possible to delay chemotherapy until after the baby is born.
- For a woman who needs treatment sooner, the doctor may suggest starting chemotherapy after the 12th week of pregnancy when the fetus is beyond the stage of greatest risk.
- In some cases, termination of the pregnancy may be considered.

If you or your partner is considering pregnancy after completing chemotherapy, discuss the matter with your physician.

But for unborn African babies, AIDS doctors such as Dabis and Newell propose that a lesser safety standard be applied than for white ones in the first world, throwing to the wind the well-settled medical convention that growing human foetuses should not be exposed to cytotoxic nucleoside analogue drugs generally, and not during the first term in particular – especially since chemotherapeutic drugs in pregnancy have been shown in animal studies to cause cancer in offspring: in the case of AZT specifically, in the studies we surveyed in our last letter, and chemotherapeutic drugs generally, as Llombart found way back in September 1976, reporting in *Das Osterreichische Kneipp-Magazin* (3(3):72-7) **Tumoral drugs as possible blastogenic agents: the problem of anti-blastic medication.**

Llombart made ‘careful note ... of the possible appearance of tumors throughout the lives’ of 1264 rats born to mothers treated with double the usual kg/day human dose of a range of standard chemotherapy drugs. In an incidence of tumour development of up to 37.42 % following transplacental foetal drug exposure, ‘The benign forms predominated in all the tumors produced, but with some of the drugs the malignant varieties produced were made as 39.3% of the tumors. The location and type of tumors were variable; there being cutaneous, glandular, mammary, hepatic, renal, and tumors of the nervous system; there were also tumors of epithelial, connective and nervous variety.’

That chemotherapeutic drugs similar to AZT and 3TC cause permanent late-onset brain and neurological damage even among adults with fully formed brains and nervous systems has been reported in a string of recent papers.
Van Dam et al. began by reporting **Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy** in February 1998 in the *Journal of the National Cancer Institute* (90(3):182-3). Their paper in *Cancer* a year later, **Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma** (90(3):182-3), reported the ‘late effects on neuropsychologic functioning of CMF adjuvant chemotherapy’ years after cessation of treatment, and found objective evidence of

Impairment in cognitive function ... in 28% of the patients treated with chemotherapy compared with 12% of the patients in the control group ... Cognitive impairment following chemotherapy was noticed in a broad domain of functioning, including attention, mental flexibility, speed of information processing, visual memory, and motor function.

Other confirmatory studies have followed, most recently by Wefel et al. in June this year in *Cancer* (100(11):2292-9). The title of their report augurs grimly: **The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial.**

All these findings are consistent with those of the French Paediatric AIDS Study Group, which reported crippling, sometimes fatal, neurological injuries to babies exposed to AZT and 3TC in utero and post partum – findings to be expected in the light of Busidan’s et al. report in the *Journal of Pharmacological Science* in December 2001 (90(12):1964-71) concerning **AZT distribution in the fetal and postnatal rat central nervous system:**

The distribution of 3’-azido-3’-deoxythymidine (AZT, zidovudine), an antiviral drug used in the treatment of human immunodeficiency virus, was investigated in gestation day-20 (G-20) fetuses and in postnatal day-20 (PND-20) rats. At both ages, a single dose of 150 mg/kg (1.78 mmol/kg) AZT was administered orally along with tracer amounts of 14C-AZT, and rats were randomly killed at 15, 30, 60, 120, or 240 min after dosing. The fetuses, brains, and spinal cords were processed for autoradiography. ... In the G-20 rats, the brain showed higher levels of AZT than spinal cord only at the 30-min sample time, whereas in the PND-20 rats, greater radioactivity was found in the spinal cord up to the 240-min sample time. This pattern of AZT distribution in the central nervous system may hypothetically be attributed to the postnatal development of an organic anion carrier system believed to be responsible for transporting AZT from the brain to the blood, resulting in relatively greater overall exposure of the spinal cord to AZT than observed in the brain.
It’s really no coincidence that the CDC should have added ‘AIDS dementia’ to its list of AIDS defining illnesses in the same year, 1987, that AZT was licensed in the US as an AIDS drug, in the light of Bacellar’s et al. report in the October 1994 issue of *Neurology* (44(10):1892-900) that

the risk of developing HIV dementia among those reporting any antiretroviral use (AZT, ddI, ddC, or d4T) was 97% higher than among those not using this antiretroviral therapy. ... In addition, the findings of our analysis seem to confirm previous observation of a neurotoxic effect of antiretroviral agents ... linked ... to the development of toxic sensory neuropathies, usually in a dose-response fashion.

The neurological injury of children reported by the French Paediatric HIV Infection Study Group in 1999 and 2003 was consistent with this finding.

Relying blindly on the incompetents responsible for producing the WHO Guidelines, Council’s recent recommendation that HIV-positive pregnant women be given AZT has put thousands of South Africans, mostly black, mostly poor, at risk of suffering the same iatrogenic tragedy.

Council’s demonstrated fealty to the pharmaceutical cartel at the expense of the welfare of our South African people, mostly black, mostly poor, underscores the urgent need for a radical overhaul of its composition. In this regard, we think an observation made by KwaZulu-Natal Health MEC Dr Zweli Mkhize a few years ago rather apposite: ‘There is in this country a long history of whites telling us what do with our bodies ... There has always been this debate about Africans determining what is right for Africans, not whites.’

It’s a curious coincidence that the IAS Ghent Group’s caring mission into Africa on behalf of GlaxoSmithKline and Boehringer Ingelheim should sue out from Belgium – as does *Médecins Sans Frontières* on the same drug-dealing trip. Of all Europe’s colonial projects in nineteenth and twentieth century Africa, Belgium’s Congo was the most callously murderous, killing, according to the best scholarly estimates, about ten million Africans.

As he raped the country, Leopold II (honorary president of the British Aborigines Protection Society) sold his depredations to the believing world as a Christian crusade to secure the ‘abolition of the traffic in slaves’, an involvement motivated by ‘the noble aim of rendering lasting and disinterested services to the cause of progress’.
Some might see the same criminal energy pumping behind it, the same metaphysical corruption driving it. We do. *Plus ça change, plus c’est la même chose.* The horror, the horror.

Yours faithfully

ADV ANTHONY BRINK
CONVENER AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP
Cc: The South African government, all provincial Health MECs, media and other interested parties.

IMPORTANT POSTSCRIPT:

After gross irregularities both in the conduct of the HIVNET 012 nevirapine trial in Uganda and the US National Institutes of Health’s subsequent attempt to whitewash them in its ‘Remonitoring Report’ were brought to the attention of the Oversight and Investigations Subcommittee of the Energy and Commerce Committee of the US House of Representatives in March this year, the committee ordered the National Institutes of Health to submit to an independent investigation of both the trial irregularities and the cover-up. The Institute of Medicine, a branch of the National Academy of Sciences of the United States of America, was tasked to carry it out in about June. Its website currently notes:

> At the request of the National Institutes of Health (NIH), the Institute of Medicine (IOM) is conducting an independent review of the HIVNET 012 perinatal HIV prevention trial. ... The NIH has asked the IOM to review methodological and data interpretation issues related to protocol design, data collection, recordkeeping, quality control, and analysis. The committee will assess the impact of these issues on the validity of overall findings and conclusions of the trial.

On 21 September 2004 the National Whistleblower Center (‘NWC’) in Washington wrote to the IOM, raising rampant conflict of interest in the IOM panel, and other serious matters compromising the enquiry. A copy of its letter is annexed [*]. (Two members of the panel reacted by resigning; the other issues remain to be resolved.)

The pressing local relevance of these developments in the US – even though Council has rejected both the HIVNET 012 study and the NIH’s subsequent defence of it – arises from reference in the NWC’s letter to a plethora of ‘unreported adverse that were not recorded, as the principal investigators admitted to the Westat auditor’ and the fact that ‘the study physicians evaluated adverse events often on the basis of third hand
descriptions from non-physicians and without personally examining all patients’.

HIVNET 012 is the study on the basis of which Council specially registered nevirapine as both safe and effective for administration to women in labour and their newborn babies in South Africa, and it was the lynchpin of the Treatment Action Campaign’s successful case against our government in the High and Constitutional Courts, forcing it to supply the drug for this indication.

After subsequently rejecting HIVNET 012, as well as the NIH’s attempt to save the study in its ‘Remonitoring Report’, Council put Boehringer Ingelheim on terms to come up with other evidence of safety and efficacy to warrant the continued special registration of the drug. The time allowed the company has long come and gone. In our first letter in June we asked what Council was doing about this. We’re still waiting to hear.

The HIVNET 012 trial overseers’ admission that numerous adverse events went unrecorded, and that those adverse events that were recorded were often based on hearsay only, underscores the urgency of the need for Council to determine its review of its continued registration of nevirapine for even single-dose perinatal use. The safety data reported in HIVNET 012, on the basis of which Council specially registered nevirapine for perinatal use in South Africa, bad as they were, have turned out to be utterly corrupt.

The continued registration of the drug for perinatal use is indefensible. In the circumstances, why has Council not revoked the special conditional license it granted Boehringer Ingelheim to market nevirapine for administration to women in labour and their newborn babies?

Has everyone gone fishing?

*See Part Nine of The trouble with nevirapine in paperback or online at www.tig.org.za*
Thalidomide victim

‘Distavel [thalidomide] can be given with complete safety to pregnant women and nursing mothers without adverse effect on mother or child. ... Outstandingly safe, Distavel has been prescribed for nearly three years in this country [UK]. ... a harmless, safe and effective sedative with no side effects. ... Harmless even over a long period of use ... completely harmless even for infants.’

British Distillers (Biochemicals) plc c.1961.

‘The piperidinedione hypnotic thalidomide was responsible for thousands of children with disastrous defects such as absence of limbs. This occurred especially in Germany. Pregnant women ingesting a single hypnotic dose of the drug between the twenty-fourth and thirty-sixth day of their pregnancy have delivered severely deformed babies.’

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

I refer to our meeting at your offices in a different connection last Thursday, at which I enquired whether there was any prospect of Council ever responding to our letters. You answered that a reply had been prepared and was awaiting signature. I informed you that as our seventh letter, sent up to you by courier on the Friday before (8 October 2004), contained crucial additional research data and other information pertinent to the matters in question, we hoped that Council would consider it before arriving at any conclusions. I record that I handed you an extra copy.

This is to confirm that you agreed to see to it that Council considers our seventh letter before issuing its response.

As we mentioned in our seventh letter we intend commencing proceedings to have Council publicly called to account for its failure to discharge its official function to the people of South Africa, namely to protect them from the marketing of harmful products by the pharmaceutical industry. In anticipation of a considered response from Council to our correspondence, however, we’ll put our approach to the Public Protector on hold for one month.

This month five years ago, on 28 October 1999, after reading my survey of the medical literature published to date on the exceptionally dangerous toxicity of AZT in *Debating AZT: Questions of Safety and Utility*, President Mbeki called attention to the threat to public health posed by AZT in his address to the National Council of Provinces and directed that an enquiry be conducted into the issues raised in the subtitle. (The
manuscript was updated and published a year later as *Debating AZT: Mbeki and the AIDS drug controversy.*

What emerged at the time from public statements made by several leading AIDS experts was that President Mbeki was much better informed in the subject than they were. Then MRC president William Makgoba boasted of being a total ignoramus: ‘I’ve read nothing in the scientific or medical literature indicating that AZT should not be given to people.’ So did his similarly bone idle AIDS research chief at the MRC, Salim Abdool Karim: There is ‘no new evidence in the medical literature in the last year on the adverse effects of AZT’.

As Council proceeded to disgrace itself by botching the enquiry that President Mbeki had entrusted it to conduct, its then chairperson, Helen Rees, let on that its members were no less uninformed and clueless than their medical eminences aforementioned: ‘The drug being out there is justified,’ she announced, delivering Council’s all-clear verdict – as if President Mbeki had been carrying on about nothing like Henny Penny.

Indeed, that Council hadn’t taken President Mbeki’s formally raised concerns seriously emerged from a patronising statement that Rees made to *Newsday* on 11 July 2000: ‘... most researchers ... concluded long ago that the HIV-fighting value of antiretroviral drugs (such as AZT) were worth the awful side-effects they can trigger ... case closed. So what gives with South Africa? You can’t just view this matter as a health issue, South Africans wearily explain. You also must see it as a political issue. It’s all wrapped up in the South African liberation movement, observed Dr. Helen Rees, who chairs South Africa’s Medicines Control Council. Today, nothing is beyond debate – and that is a heady thing for this long-repressed nation. “I don’t have a problem with someone who says, ‘Go back and look at this again,’ Rees said, “because people need room to learn and grow.”’

The pity of it was that the English immigrant – who presumed to understand and elucidate the troubled psychological dynamics behind the liberation politics of the President’s intervention, and who wearily indulged his ‘need’ for ‘room to learn and grow’ – felt above taking her own advice.

Shortly after President Mbeki alerted the people of South Africa to the fact that ‘There ... exists a large volume of scientific literature alleging that, among other things, the toxicity of this drug is such that it is in fact a danger to health’, Dr Tshabalala-Msimang made a number of public statements, both in Parliament and to the media, that were supportive of his concerns, particularly in regard to the use of AZT during pregnancy.
Council might find it instructive to reconsider them in the light of research findings published since.

‘There is no substantial data that AZT stops the transmission of HIV from mother to child. There is too much conflicting data to make concrete policy.’ Any of Council’s members who have actually troubled themselves to read Papadopulos-Eleopulos’s et al. exhaustive examination of the subject published in October 2001 that we sent up to you, *Mother to Child Transmission of HIV and its Prevention with AZT and Nevirapine: A Critical Analysis of the Evidence*, will have seen the fallacy identified by Dr Tshabalala-Msimang in her first sentence meticulously and comprehensively taken to pieces. The monograph closely discusses the ‘conflicting data’ alluded to in her second sentence, and lays it hopelessly bare.

‘I want to dispel this myth [that the only proper approach to AIDS is to supply AZT] because it is absolutely not true. The pharmaceutical industry and those who have a vested interest in the drug industry fuel this propaganda.’ Our last letter unveiled the pervasive influence of the ‘drug industry’ over WHO policy-making, as well as of ‘those who have a vested interest in it’. We’ll be talking another day about the drug industry’s iron grip on medical opinion in our country’s medical schools where Council’s ‘external consultants’ work, and how these people function in clandestine cabals, making decisions affecting our country’s people unaccountably, and how they connive to choose their industry-friendly chums to join them on Council, studiously snubbing any academic colleagues who might rock the industry’s boat, no matter how distinguished their qualifications. And although Council keeps its membership list as secret as the Skull and Bones’s – yes, ten years into our open democracy – we’re busy working on smoking them out individually for public exposure and ignominy. By way of full-page ads in the newspapers and email to our vast mailing list – and a promise we make is a promise we keep.

‘There is a lack of information on how the drugs affect these children over time.’ Since Dr Tshabalala-Msimang made that statement in late 1999, a profusion of published research data, set out in our letters, have provided new ‘information on how the drugs affect these children over time’. Horribly.

‘We have to be very cautious ... so that we do not look back 10 to 15 years down the line and find that we had exposed ... our people to a dangerous drug. ... We have to be very cautious, very sensitive.’ Numerous studies published in the five years since this statement was made have unequivocally confirmed Dr Tshabalala-Msimang’s worst apprehensions:
AZT is an extremely ‘dangerous drug’, especially when used in pregnancy. But insensitive to these new findings, Council has thrown all caution to the wind in recommending AZT for administration to pregnant women, mostly black, mostly poor.

‘Could you with a clear conscience introduce those toxic drugs to a woman and her child? I say no.’ Council’s members, in recommending AZT to mostly black, mostly poor South African pregnant women and their newborn babies, have demonstrated that they subscribe to an entirely distinct set of moral values from those of our President and Health Minister. It’s obviously high time they were kicked out like the drug cartel cronies fingered by the Dukes Committee, and replaced with scientists responsive to public concern about the industry’s toxic merchandise – particularly when expressed, not by politically bankrupt opposition party hacks on drug company retainers, but by a visionary leader of incomparable stature in the modern world.

‘Until we are convinced that the drug AZT is safe, as a responsible government we will not move in that direction.’ Research findings reported in the five years since this statement was made have consistently shown, as Brinkman et al. had just noted in Lancet two months earlier (1999 Sep 25;354(9184):1112-5), that AZT is ‘much more toxic than we considered previously’. And yet ten years ago Lenderking et al. had already reported in the New England Journal of Medicine (1994 Mar 17;330(11):738-43) that just 500 mg of AZT given daily to ‘asymptomatic patients’ causes ‘severe side effects’ that are ‘life threatening in some cases’. But the cartel’s stooges advising the WHO and Council propose that asymptomatic pregnant African women, mostly black, mostly poor – who have been declared HIV-infected by AIDS doctors on the strength of a useless antibody blood screening test that reacts positively to past pregnancy among about seventy other documented cross-reacting conditions and diseases – be fed not just ‘life-threatening’ AZT during their pregnancies, but equally toxic 3TC and nevirapine as well. To their newborn babies too. Since they’re the experts.

‘AZT is a confirmed carcinogen. ... The fact is that some of the mice [given AZT] have contracted cancer. It attacks bone marrow. It is very toxic.’ Five years on, notwithstanding the accumulation of further consistent research reports in this regard that we canvassed in our letters, Council’s members have disregarded them all and have chosen to accord themselves with the position taken by famed AZT advocate Charlene Smith in her glittering retort to Dr Tshabalala-Msimang’s above-cited warning: ‘Stop giving AZT to the damn mice and start giving it to people.’
With such dumb blondes as Glenda Gray, Helen Rees and Charlene Smith calling the AIDS drug policy shots in South Africa, maybe Michael Moore should fly in and document their performance as his next project and call it Stupid White Women. (He’d find no shortage of them in the virology faculties of our country’s medical schools either.) But seriously, having regard to the corpus of published AZT toxicity data drawn to Council’s attention in our correspondence, we propose that any of its members still recommending the prescription of AZT to pregnant women and their newborn babies, mostly black, mostly poor, are equally ignorant, lazy, simple, corrupt or depraved.

Dr Miklos Nyiszli, a Jewish pathologist interned at Auschwitz and forced to conduct autopsies on other prisoners killed by Dr Josef Mengele in the course of his Nazi medical experiments, described the sort: ‘Among all criminals and murderers, the most dangerous type is the criminal physician.’ Since AZT has been shown to kill children exposed to it in the womb, and neurologically and otherwise seriously harm others, those intransigent members of Council, who, notwithstanding notice of the dreadful research data traversed in our correspondence, persist in putting the commercial interests of the pharmaceutical cartel and their own face above the safety of the South African public, might reflect on whether this cap fits them too.

We look forward to Council’s promised response to our letters, including our seventh. Be sure to pass this eighth one on too, please. Would you confirm that you have done so in writing? As we’ve mentioned, we expect having to go beyond Council’s invested experts to set this mess straight. Because having ignorantly contradicted President Mbeki and Dr Tshabalala-Msimang on the dangerous toxicity of AZT in 1999 and 2000, particularly concerning its use in pregnancy, and then going on in July this year to actively recommend this despite the intervening accretion of so much appalling adverse data, we honestly don’t think there’s much hope that they’ll be up to reversing themselves and publicly admitting that they have blundered big-time. Since who likes eating crow?

Yours faithfully

ADV ANTHONY BRINK
CONVENER AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP

Cc: The South African government, all provincial Health MECs, media and other interested parties.
The Chairperson: Medicines Control Council
Professor Peter Eagles
School of Pharmacy
University of the Western Cape
Private Bag X17
Bellville

Dear Professor Eagles

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

Thanks for your letter of acknowledgement in this matter, just in, dated 22 November 2004 – five months to the day since our first letter. But we were most put out to see reference to our first two letters only. In fact we sent up six more plus an addendum, as well as two substantial scientific papers in lever-arch files, which closely examine the pharmacology of AZT and nevirapine, and a PowerPoint slideshow on CD concerning the latter drug. All our submissions were hand-delivered by courier. Your people seem to have lost them. Would you make enquiries about this? Our sixth and seventh letters, which extensively analysed the AZT foetal toxicity literature, are particularly crucial to the proper determination of the safety issues we raise. The addendum amplified our sixth letter, citing more AZT foetal toxicity studies.

Assuming the worst, we enclose another complete set of our letters for you to read, as well as bound copies of the big scientific papers that we sent up, and ten CDs onto which all materials sent up to Council have been saved. Would you personally see to it that all members of Council’s sub-committee responsible for the registration and recommendation of nevirapine and AZT as perinatal anti-HIV prophylactics get a copy? We obviously can’t count on your staff in Pretoria to do this.

We note with concern your statement that ‘An independent external opinion on the scientific and clinical conclusions made in your letters has been sought by Council and is awaited.’ Who’s this guy? Has he filed a sworn conflict of interest declaration?
Aren’t Council’s members sufficiently independent? Aren’t they able to weigh the issues and make up their own minds as their appointments require? It seems that Council has abdicated its statutory responsibility to apply its collective mind to the drug safety issues raised in our submissions, and has unlawfully asked someone else to do its job for them. We’ll be taking this point formally if needs be.

We note your mention of plans to establish a Pharmacovigilance Centre at the University of the Free State. MEDUNSA has the same idea. This sounds all very soothing, but given the findings already made abroad about the horrible effects of AZT on unborn and newly born babies, we think Council should act immediately to pull this drug, and not wait and see how many more children, mostly black, mostly poor, are killed or maimed in South Africa too, before doing so. Did we need a new research institute in this country to find out how many babies were being born deformed here before dumping thalidomide? Or did South Africa heed the early evidence overseas?

In conclusion, two recent developments have taken place that afford Council a face-saving exit from the bog it waded into in recommending on 12 July that pregnant women continue taking nevirapine – in combination with AZT.

First: Associated Press is about to blow the whistle on the deliberate suppression by top US NIH officials of two reports concerning serious toxic side effects and unreported deaths in the HIVNET 012 nevirapine trial, which the NIH had financed, so as not to upset President Bush’s $500 million mission to fight AIDS in Africa, centring on the provision of nevirapine. Which he proceeded to announce on 19 June 2002, having been kept in the dark about the dangers of the drug:

This major commitment of my government to prevent mother-to-child HIV transmission is the first of this scale by any government, anywhere. We will support programs that administer a single dose of nevirapine to the mother at the time of delivery, and at least one dose to the infant shortly after birth. This therapy reduces the chances of infection by nearly 50 percent.

I have a copy of the draft AP article, for which I was interviewed, and was informed that it will be the first of an intended series on the drug, the next major drug scandal.

Now that Council has been alerted to this deadly fraud on us by the Americans, we suggest that it direct some enquiries about it to the NIH. We were impressed by its rejection of the NIH’s attempt to dupe it into accepting HIVNET 012 by way of its ‘Remonitoring Report’ snowjob,
and trust that it will be as impervious to the dissembling of these crooks a second time round. The issues are identified in a letter written by the National Whistleblowers Center in Washington, annexed to our seventh letter.

If Council doesn’t take this up with the NIH, we will see to it that it is very publicly asked later on why it turned a blind eye to this critical information provided to it about the hazards of the HIVNET 012 nevirapine regimen for South African women and their babies, mostly black, mostly poor.

Second: In a major review of data collected between 1986 and April 2004, the European Collaborative Study has just reported that AIDS drugs cause a ‘substantially increased risk of severely curtailed pregnancy [i.e. critical prematurity] ... coupled with a very high neonatal mortality rate’. (Thorne et al. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS 18: 2337-2339, 2004.)

In the light of these findings, on top of all the others we’ve reviewed, we think that only a moron or a really malevolent racist would continue recommending that pregnant women in South Africa, mostly black, mostly poor, be given AZT combined with nevirapine during their pregnancies. What do you reckon?

The Mail&Guardian isn’t likely to share this view, though. You might have seen our full-page piece on the back of its World AIDS Day supplement, which the paper had invited us to place, asking ‘Why should South Africans continue to be poisoned with AZT?’, and pointing out that

Hundreds of studies have found that AZT is profoundly toxic to all cells of the human body, and particularly to the blood cells of our immune system.

Numerous studies have found that children exposed to AZT in the womb suffer brain damage, neurological disorders, paralysis, spasticity, epilepsy, other serious diseases and early death.

M&G editor Ferial Haffajee’s response to a slew of angry letters about this, three of which protested that the statement of such unspeakable facts would actually ‘kill people’, was that our piece ‘should not have been carried’ and such writing ‘will not be carried in the Mail&Guardian in future’.

After agreeing with this writer to publish a reply, she spiked it minutes before going to press. When we phoned to enquire about this change of tune, we got M&G Chief Operations Officer Hoosain Karjeiker on the
line. He explained that what was objectionable in our reply was our reference to ‘the side effects of extremely toxic pharmaceutical drugs like AZT and nevirapine’. ‘We are proponents of AZT,’ he said. ‘Once again the ad casts aspersions on AZT and nevirapine.’ ‘Do you mean it’s unacceptable to state that AZT is toxic?’ we asked incredulously. ‘Yes,’ he replied; it’s ‘dissident’.

Editor Haffejee phoned about an hour later with more of the same:

Our newspaper has been at the forefront of the push for antiretrovirals in this country. Our brand has suffered because of your ad two weeks ago. The new ad contains the same message, albeit not as strong. Publishing it will continue to damage our brand.

Run by such people do you think this could be why black intellectuals and politicos here generally refer to the Mail&Guardian as the ‘Mail and Garbage’?

Can we expect a better show from the MCC now that it’s been given all the facts?

Yours faithfully

ADV ANTHONY BRINK
CONVENOR AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP

Cc: The South African government and other interested parties; The Registrar: MCC.
18 January 2005

The Chairperson: Medicines Control Council
Professor Peter Eagles
School of Pharmacy
University of the Western Cape
Private Bag X17
Bellville

Dear Professor Eagles

MCC Review of its Special Registration of Nevirapine for Perinatal Administration, and its Recent Recommendation that Nevirapine be Administered Together with AZT in Perinatal Applications

I write to draw Council’s attention to the latest findings of brain damage among children exposed to AZT and 3TC in utero, reported by Poblano et al. at the end of last year. Enclosed are both the Pubmed abstract of their paper, and the full text, which the authors kindly sent me.

I also enclose Parts Nine and Ten of *The trouble with nevirapine*, which I wrote in December.

Part Nine details the fraudulent suppression by the US NIH of the independent audits that found HIVNET 012 to have been a complete shambles, and it gives the inside story that I got from the senior NIH staffer who blew the whistle on the scandal.

Part Ten lets the wind out of another recently reported mother to child AZT and nevirapine clinical trial, the bad news about which the deputy editor of the *South African Medical Journal* shamefully suppressed. Just so you know when Boehringer Ingelheim comes trying to rely on this junk study too.

Please pass the information on to the responsible sub-committee.

Yours sincerely

ADV ANTHONY BRINK
CONVENER AND NATIONAL CHAIRMAN
TREATMENT INFORMATION GROUP
Annexure:


The purpose of this study was to determine whether there were differences in Brainstem Auditory Evoked Potential (BAEP) waves and interval interwaves in a group of Zidovudine (AZT) alone or AZT plus Lamivudine (3TC) prenatally exposed infants; compared with a group of infants not exposed to antiretroviral drugs. Results could provide an index of neurotoxicity in newborns. Infants were included in the study if they were exposed prenatally to AZT alone or AZT plus 3TC. Comparison of wave latencies showed significant delay of wave I and I-III interwave interval in the AZT-3TC-treated group.

DISCUSSION ... Infants with AZT/3TC exposure displayed less-well-developed BAEP within lower brainstem regions, suggesting subclinical dysfunction in these auditory centers within the brainstem. To our knowledge this is the first study to recognise brainstem toxicity of antiretroviral treatment in perinatally exposed newborns. One possible explanation of this fact is that AZT/3TC cause mitochondrial damage in cochlear hair cells [19] and in brainstem neurons, such as that observed in adult patients. Our data suggested that antiretroviral therapy has a preferential effect in the lower brainstem neurons and in auditory nerve and thus may represent the targets of drug damage. The results presented here suggested the possibility of antiretroviral neurotoxicity during a critical period of auditory system development.

Reference 19 is to Marra’s et al. positive finding concerning Hearing loss and antiretroviral therapy in patients infected with HIV-1, reported in *Archives of Neurology* (1997 Apr;54(4):407-10): ‘Hearing loss is common among HIV-infected individuals and is associated with antiretroviral therapy in those aged 35 years or older.’
Afterword

He was exceptionally knowledgeable about medicine. From the scientific point of view, he was the only SS officer there of quality. For me, he was very worth talking with. He was an ideologue, body and soul. Never any emotion; he showed no hate or fanaticism ... and as the Jews were going to die anyway, he saw no reason not to use them first for medical experiments.

Hans Münch, acquitted at the Auschwitz doctors trial in Cracow, Poland, on 22 December 1947, speaking of his fugitive colleague Josef Mengele

On 24 February 2005 the US Public Health Service released its updated Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States. The Recommendations were drawn by a bunch of AIDS doctors (all MDs), whose ‘Executive Secretary’, and probable principal author, was Lynne Mofenson, a prominent apologist for the administration of AZT to pregnant women. The Recommendations essentially echo the WHO Guidelines – indeed, Mofenson was a consultant in their formulation. To read them is to recall Münch speaking about Mengele: one is struck by the AIDS doctors’ single-mindedness, their relentlessness, their absolute determination to do what they believe must be done for these people with the bad blood. Mostly people of colour. And irrespective of the human cost.

The Recommendations assert that ‘pregnancy is not a reason to defer standard therapy’ (AZT and similar drugs), notwithstanding that AZT is classified by the FDA as a ‘C’ class drug, meaning that the potentially harmful effects of the drug on the unborn child remain unknown, as the Recommendations explicitly concede: ‘Data to address many of these considerations [‘the potential for adverse short or long-term effects on the fetus and newborns’] are not yet available.’ Except that in the last few years ample evidence has been reported that AZT may be profoundly harmful, sometimes fatally, to unborn and newly born children. To this the AIDS doctors pay lip service in their Recommendations, warning that ‘Information included in these guidelines may not represent approval by the Food and Drug Administration (FDA) or approved labelling for the particular product or indications in question. Specifically, the terms “safe” and “effective” may not be synonymous with the FDA-defined legal standards for product approval.’ In view of this, the Recommendations say, ‘offering antiretroviral therapy to HIV-1 infected women during
pregnancy … should be accompanied by a discussion of the known and unknown short- and long-term … risks of such therapy to infected women and their infants.’ In other words, AIDS doctors should explain to worried mothers bearing babies inside them that they’re swallowing extremely toxic chemotherapy that could kill, seriously injure or neurologically damage their children for life in a manner that won’t necessarily be clinically obvious. Of course they never do explain this.

A striking illustration of the dismal quality of the expertise of the doctors who drew the Recommendations lies in the fact that they proceeded from a decade-old fallacy, thoroughly debunked in the scientific press, concerning ‘the pathogenesis of HIV-1’, and they entirely ignore the official reversal of the ‘hit early, hit hard’ treatment approach announced by the US Department of Health and Human Services on 5 January 2001.

So we have the Recommendations claiming ‘substantial advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of persons with HIV-1 disease. These advances have resulted in changes in standard antiretroviral therapy for HIV-1. More aggressive combination drug regimens that maximally suppress viral replication are now recommended.’ These statements refer to Ho, Wei and Shaw’s novel model of HIV pathogenesis, proposed in the mid-nineties, that HIV isn’t a slow virus (a lentivirus) as had been supposed for the preceding ten years, but is instead a rapidly proliferating one best defeated by aggressive ARV drug treatment. The new ‘understanding’ was almost immediately exposed by the AIDS experts themselves as nonsense (leaving a theoretical vacuum in its place), although it took another five years for the ‘aggressive’ treatment approach based upon it to be officially reassessed and abandoned.

The Recommendations note on their front cover that ‘It is emphasized that concepts relevant to HIV management evolve rapidly.’ Indeed so, but they are evolving in the opposite direction from what the AIDS doctors suggest in their Recommendations. The latest development in this reverse direction appears in the British HIV Association’s draft revised guidelines published on 26 April 2005. Written by leading UK AIDS doctor Professor Brian Gazzard, the BHIVA guidelines warn that ‘as evidence accrues that AZT (zidovudine, Retrovir) is associated with lipoatrophy [wasting, due to the drug’s mitochondrial toxicity], the guidelines move away from firmly recommending an AZT-containing regimen as part of a nucleoside backbone’.

Tardieu et al. of the French Pediatric HIV Infection Study Group (Blanche, Barret et al.) reported in the same month in the American Journal of Neuroradiology (26(4):695-701) that
Mitochondrial dysfunction has been reported in HIV-negative children perinatally exposed to zidovudine, a drug often used in HIV-seropositive mothers during pregnancy. The purpose of this study was to determine the incidence of cerebral MR imaging findings in HIV-uninfected children exposed to zidovudine who present with unexplained neurologic symptoms. … Images observed in children with antiretroviral-induced mitochondrial dysfunction are similar to those observed in congenital mitochondrial diseases.

As Brinkman explained more than five years ago (Lancet (1999 Sep 25; 354(9184):1112-5), AZT and related drugs are much more toxic than we considered previously. … The layer of fat-storing cells directly beneath the skin, which wastes away … is loaded with mitochondria [intracellular organelles crucial to energy metabolism] … other common side effects of [AZT and related drugs are] nerve and muscle damage, pancreatitis and decreased production of blood cells … all resemble conditions caused by inherited mitochondrial diseases.

Despite this, the American AIDS doctors firmly recommend in their new Recommendations that in ‘resource-constrained settings’ such as South Africa ‘to prevent perinatal transmission, ZDV [AZT] chemoprophylaxis should be incorporated into the antiretroviral regimen’. Which is to say pregnant women should swallow it regardless. Of how it has been shown to poison them and their babies.

On 28 October 2005 we finally received MCC chairman Professor Peter Eagles’s response (dated five weeks earlier) to all our correspondence. Absolutely nothing to worry about, he said:

your documentation has not shown that the potential risks of adverse effects of the antiretroviral agents in question are greater, more serious, or on a larger scale than the risks of complications from HIV-infection and its adverse effect on the lives of babies and children. Information which has become available subsequent to the Medicines Control Council (MCC) resolution of 02 July 2004 has also not changed the overall assessment of the risk of HIV-1 infection compared to the adverse effects of antiretroviral agents in PMTCT. (For example, we refer you to the frequently updated guidelines on the “Aidsinfo” website: www.aidsinfo.nih.gov.)

These are the Recommendations discussed above. The MCC’s anonymous ‘expert’ appointed to consider our ‘documentation’ had disposed of the matter by simply referring to the Americans.

A few days later, on 3 November, AIDSmap News summed up the latest paper regarding the harm AIDS drugs do to unborn children, ‘Does
exposure to antiretroviral therapy affect growth in the first 18 months of life in uninfected children born to HIV-infected women?’ reported by the European Collaborative Study in the *Journal of Acquired Immune Deficiency Syndromes* (40 (3): 364-370):

Children born to HIV-positive women who take antiretroviral therapy (ART) during pregnancy are significantly smaller in terms of height, weight and head circumference compared with children born to HIV-positive women not on ART, or who took monotherapy, according to the results of a European study examining the effects of ART on uninfected children’s growth up to the age of 18 months.

Having trouble thinking straight, like all AIDS doctors believing they’re going about a higher purpose in saving babies from their mothers’ germs (just as Nazi doctors went about theirs in the same mystical thrall, although not paid the same millions for doing so), the European Collaborative Study group were unable to acknowledge that they were actually doing something terrible: first they said the stunted growth was ‘unlikely to be clinically relevant at this age’ (eighteen months); then they pretended that it may be, but they weren’t sure: ‘the subsequent clinical implications of this finding are unclear’.

But they are clear. ‘Growth faltering, particularly stunting, may adversely affect a child’s quality of life, especially once they reach adolescence,’ noted Newell et al. in *Pediatrics* in January 2003 (111(1):e52-60) – claiming in their paper that AIDS drugs don’t actually stunt growth; no, the cell-killing chemicals help children grow!

The trouble the European Collaborative Study’s AIDS doctors have seeing what they’re doing is underscored by their previous report on 21 October 2004 in *AIDS* (18(15):2009-17):

> Antiretroviral drugs (ARV) as prophylaxis to prevent mother-to-child transmission of HIV results in decreased haematological parameters during and shortly after exposure, with recent data suggesting a more prolonged inhibition of haematopoiesis until at least 18 months [*i.e. ARV drugs given to pregnant women cause persistent, probably permanent, bone marrow suppression, thus reducing blood cell production*]. In uninfected children … ARV exposure [before birth was] associated with reduced neutrophil count until at least 8 years of age. … CONCLUSION: A considerably longer effect of exposure to ARV was shown in uninfected children than previously thought.

Again the AIDS doctors administering the toxic drugs claim that ‘the clinical implications are not clear’ – yet it’s elementary to immunologists that ‘a decrease in the number of neutrophils in the blood … results in an increased susceptibility to infections’ as the *Oxford Concise Medical*
Dictionary puts it. A ‘neutrophil [is] a variety of granulocyte (a type of white blood cell) … capable of ingesting and killing bacteria and provides an important defence against infection.’ Could this be why babies poisoned by AZT in the womb, and immediately after birth in some cases too, have been reported in numerous studies to suffer much higher rates of serious disease and early death than unexposed babies?

Don’t ask an AIDS doctor. He’ll tell you it’s the HIV infection coming on, which his toxic drugs just weren’t strong enough to stop. Just as doctors used to blame that stubbornly resilient syphilis spirochaete for the slobbering and shambling of G.P.I. cases (general paralysis of the insane), for whom neurotoxic arsenic injections (Salvarsan) weren’t strong enough from 1910 right up until the fifties. And, given to pregnant women, not strong enough to prevent stillbirth, blindness, deafness, mental retardation, facial deformity and no end of other birth defects and illnesses.