

IN THE COMPETITION COMMISSION OF SOUTH AFRICA

In the complaint submitted by:

TREATMENT ACTION CAMPAIGN

Concerning the conduct of:

MSD (PTY) LTD

MERCK & CO., INC. AND RELATED COMPANIES

EXPERT AFFIDAVIT OF PROFESSOR ROBIN WOOD

I, the undersigned

ROBIN WOOD

do hereby make oath and state as follows:

1. In 1986, I registered with the then South African Medical and Dental Council (now the Health Professions Council of South Africa) as a medical practitioner, and again during 1990 as a Specialist of Internal Medicine. My registration number is MP 282162. I am still so registered.
2. I can be contacted at the Desmond Tutu HIV Research Centre on 021 650 6806 and care of Rene.January@hiv-research.org.za should the Competition Commission wish to obtain further information from me.
3. The facts deposed to in this affidavit are true and correct, and save where the context indicates otherwise are within my personal knowledge. To the extent that I rely on the information received from others, I believe that such information is true and correct.
4. Between 1967 and 1990, I obtained the following degrees and diplomas: Bachelor of Science in Biophysics (1st Class Hons), London University; Bachelor of

Medicine and Bachelor of Surgery, Oxford University; Masters in Medicine, University of Cape Town (UCT); Diploma of Tropical Medicine & Hygiene, Liverpool University; and Diploma of Royal College of Obstetrics and Gynaecology, London. I am also a Fellow of the College of Physicians (SA). I spent two years (1990-1992) at Stanford University Medical School, CA (USA) engaged in an "Infectious Diseases Fellowship".

5. I currently hold the position of Director of the Desmond Tutu HIV Research Centre, Institute of Infectious Disease and Molecular Medicine, UCT. Prior to this, during 2005 – 2006 I held the position of Professor of Medicine & Head of the Division of Infectious Diseases at Groote Schuur Hospital at UCT. I am a temporary advisor to World Health Organization (WHO) on second-line antiretroviral treatment (ART) guidelines.
6. I hold the following additional positions:
 - a) Visiting Scientist, Harvard University Medical School, Boston, MA (USA); and
 - b) Honorary Infectious Disease Consultant, False Bay Hospital, Provincial Administration of the Western Cape.
7. I belong to the following societies:
 - a) Royal Society of Tropical Medicine & Hygiene;
 - b) International AIDS Society;
 - c) Southern African HIV Clinicians Society (SAHCS) (founding member);
 - d) American Society for Microbiology;
 - e) Infectious Diseases Society of South Africa;
 - f) Oxford University Medical Society; and
 - g) Balliol College Medical Society.
8. I am a member of several scientific journal advisory boards. I also sit on the SAHCS treatment guidelines committee.

9. Since 1993, I have developed extensive specialist HIV/AIDS-related research and clinical experience in South Africa. I have been involved as the principal investigator for 50 HIV-related studies. I have researched and co-authored more than 160 peer-reviewed articles, and I have had 162 abstracts at national and international science conferences on HIV/AIDS treatment. I have served and continue to serve on local, provincial, national and international committees on treatment for HIV/AIDS and other infectious diseases. My abridged curriculum vitae is attached marked **Annexure RW1**.
10. Because of my clinical expertise, I am a treatment advisor to the South African Catholics Bishops Conference (SACBC) which currently has about 18 000 patients in its HIV/AIDS treatment programme.
11. I also advise the mining sector and train its doctors to implement treatment programmes for the care, management and treatment of HIV/AIDS.
12. I respectfully submit that I am by my training and experience duly qualified to express the views and opinions that I express in this affidavit. I previously submitted information to the Competition Commission in the case of *Tau and Others v GSK and Others* under case number 2002Sep226.

HIV/AIDS

13. HIV/AIDS is a progressive disease of the immune system that is caused by the Human Immunodeficiency Virus (HIV).
14. Scientific evidence, clinical trials and international consensus, show that –
 - a) when left untreated, HIV profoundly depletes the immune system and may prove fatal because of the inability of the body to fight opportunistic infections (OIs) such as tuberculosis (TB), pneumonia and meningitis;
 - b) the use of ART – also known as highly active antiretroviral therapy or HAART – substantially reduces the incidence of OIs, resulting in

substantial reductions in morbidity and mortality rates [Braitstein P et al (2006) Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low – income and high – income countries. *Lancet* 367: 817 – 824 and Palella FJ Jr et al (1998) Declining morbidity and mortality among patients with advanced HIV infection. *N Engl J Med* 338: 853 – 860]; and

- c) in general, antiretroviral (ARV) medicines cannot be considered as substitutable for each other, even within therapeutic classes.

Impact of HAART

15. Studies show that once patients are initiated on HAART, the incidence of death decreases. Studies also show that the incidence of AIDS after the initiation of HAART decreases by about ten fold.
16. Evidence indicates that without HAART, the risk of death in patients with low CD4 counts is very high. [*Short term risk of AIDS or death in people infected with HIV-1 before ARV therapy in South Africa: a longitudinal study, Badri M et al. Lancet, vol 368 October 7, 2006*]
17. Early diagnosis, clinical management, medical treatment of OIs and the appropriate use of HAART prolong and improve the quality of life of people living with HIV/AIDS.
18. HAART has revolutionised the management of HIV infection, resulting in a radical reduction in mortality and morbidity figures amongst groups with access to treatment. Additional health benefits include the reduction and/or elimination of OIs, the restoration of immune function and a reduction in infectiousness. With access to HAART, people with HIV/AIDS are able to lead longer and healthier lives. Access to ARV treatment thus results in an improved quality of life and the restoration of dignity, allowing people with HIV/AIDS who were previously ill to resume ordinary everyday activities, such as work.
19. Since 1996, HAART has been the standard of care in Europe, North America and Brazil. Scientific consensus confirms that at least three drugs should be used together to ensure maximum clinical efficacy, reduce side effects, and limit

the emergence of resistant strains of the virus. The simultaneous use of three or more drugs, including drugs from different therapeutic classes, is essential both for individual clinical outcomes and for public health protection. In short, it is necessary to have access to a combination of drug choices both within and between drug classes.

20. On 22 April 2002, the WHO issued its first set of treatment guidelines for HIV/AIDS in resource-limited settings such as South Africa. These guidelines have since been updated on numerous occasions, most recently in August 2006.
21. The WHO treatment guidelines deal with the rational use of HAART, so that treatment will result in fewer side effects, less resistance to and better tolerance of ARV medicines. They are designed to ensure that people with HIV/AIDS are prescribed appropriate combinations of medicines, to ensure that HAART is simpler to use, as well as to guide and train health care workers in HAART.
22. The WHO guidelines are regarded as a framework for countries to develop treatment guidelines. In the case of South Africa, the WHO recommendations have been used as a basis for the national treatment protocols for treating adults and children. I deal further with this below.
23. I should point out that when new evidence emerges about the effectiveness of newer drugs and/or combinations of drugs, the WHO recommendations and guidelines for treating HIV/AIDS are revised. This is why the WHO revises its treatment guidelines on an on-going basis.

The Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa (Operational Plan)

24. On 19 November 2003 the South African government adopted and approved the Operational Plan.

25. According to the Operational Plan, government's intention is to "ensure that the highest available quality of care is provided to the people of South Africa in line with international and local norms and standards" (at page 5). It also states that "care and treatment protocols will be based on international best practice" (at page 6).
26. The Operational Plan makes provision for adult and paediatric ARV regimens and routine monitoring during treatment. This has been incorporated into the national adult and treatment guidelines. Copies of these guidelines can be made available to the Competition Commission at its request.

ARV medicines

27. The primary goals of HAART are:
 - a) Improvement of quality of life;
 - b) Reduction of HIV-related morbidity and mortality;
 - c) Maximal and durable suppression of viral load; and
 - d) Restoration and/or preservation of immunological function.
28. ARV medicines target either a particular step in the life cycle of HIV or its interaction with host cells. The ARV medicines used by the public and private sector treatment programmes in South Africa inhibit one or two key viral enzymes required by HIV for viral replication, targeting either reverse transcriptase (essential for the completion of the early stages of HIV replication) or protease (required for the assembly and maturation of new HIV).
29. Reverse transcription is a process whereby single strands of viral RNA are converted into double-stranded DNA by the reverse transcriptase enzyme. This enables HIV genetic material to combine with the host cell's DNA, a process central to the replication of HIV.
30. There are two main therapeutic classes of ARV medicines that target reverse transcriptase: nucleoside analogue reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). A third therapeutic

class – nucleotide analogue reverse transcriptase inhibitors (NtRTIs) – currently only includes a single drug.

31. NRTIs and NNRTIs work in different ways to inhibit the functioning of the reverse transcriptase enzyme. NRTIs act as false substrates for the reverse transcriptase enzyme and thereby get incorporated into the growing DNA strand and so terminate further growth of the DNA copy of the viral RNA. NNRTIs bind directly to the reverse transcriptase enzyme thereby interfering with ability its function.
32. The combination of HIV genetic material together with host cell mechanisms ultimately results in the production of the components necessary for assembly of HIV. The viral proteins produced by the above process are initially in a long precursor strand, which is subsequently cut into individual proteins by the protease enzyme. All the components of the virus are assembled and bud from the host cell. These processes result in the development of new infectious viruses.

ARV medicines in South Africa

33. The ARV medicines currently available for use in South Africa can be divided into the following therapeutic classes:
 - a) NRTIs: zidovudine (AZT), lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), stavudine (d4T) and didanosine (ddl);
 - b) NtRTIs: tenofovir disoproxil fumarate (TDF);
 - c) NNRTIs: nevirapine (NVP) and efavirenz (EFV); and
 - d) Protease inhibitors (PIs): lopinavir (LPV), ritonavir (RTV), nelfinavir (NFV), indinavir (IDV), saquinavir (SQV) and atazanavir (ATZ).
34. In South Africa, some ARV medicines are also available in fixed-dose combination (FDC) form. In addition to the combination of LPV and RTV (LPV/r, which is the only form in which LPV is manufactured internationally) and TDF/FTC (the only form in which FTC is marketed in South Africa, although it is

available as a stand-alone product outside of the country), the only combinations currently available in South Africa are:

- a) AZT/3TC;
- b) 3TC/ABC;
- c) AZT/3TC/ABC; and
- d) d4T/3TC/NVP.

- 35. Certain combinations of ARV medicines – such as AZT/3TC/NVP, TDF/FTC/EFV, TDF/3TC/EFV and d4T/3TC – are available for use in countries other than South Africa.
- 36. There are a range of other ARV medicines – such as fosamprenavir, tipranavir, enfuvirtide, darunavir, raltegravir and maraviroc – that are available elsewhere but have yet to be registered for use in South Africa.
- 37. A few ARV medicines – such as amprenavir and zalcitabine – are no longer available for use anywhere. In addition, all stock of one ARV medicine – nelfinavir (NFV) – was recently recalled as a result of product contamination.
- 38. In the public sector, a limited number of ARV medicines are available for treating HIV infection: d4T, 3TC, NVP, EFV, AZT, ddl, LPV/r, ABC and RTV.

National ARV treatment guidelines

- 39. According to the national adult treatment guidelines, two ART regimens are recommended for use in South Africa. This applies to both the public and private sector:
 - a) Regimen 1a: d4T + 3TC + EFV;
 - b) Regimen 1b: d4T + 3TC + NVP; and
 - c) Regimen 2: AZT + ddl + LPV/r.

40. It is necessary that the private sector (including donor funded community treatment programmes) conforms to the national treatment guidelines. This is so for two reasons:
- a) In order to ensure that the country as a whole complies with best practice and conforms to a single clinical norm; and
 - b) In order to prevent drug resistance – this is in the event that a private sector patient has to be moved into the public sector. Here, the availability of a suitable drug regimen should not be compromised because the patient would have been on a regimen recommended as part of the national treatment guidelines. Examples of this are where a worker is retrenched or dismissed or where a donor-funded programme transfers patients to the public sector because it can no longer fund a treatment programme.
41. In my experience, the private sector usually does conform to the national treatment guidelines.
42. The current treatment guidelines are in the process of being revised by the national Department of Health and will incorporate newly available drugs.

First-line HAART regimens

43. The first-line regimens in adults and adolescents all consist of a dual NRTI component complemented by a potent third drug, usually either an NNRTI or a PI.
44. The advantage of a dual NRTI plus NNRTI regimen is that the regimen is potent and well tolerated.

Changing HAART and second-line regimens, and limiting factors in this regard

45. HAART may need to be changed because of toxicity, patient intolerance or treatment failure. Toxicity relates to organ dysfunction. Intolerance relates to

significant drug side effects. Treatment failure relates to a regimen that is not able to suppress the viral replication.

46. If the reason for change is related to toxicity or intolerance, a drug switch may be necessary.
47. If a change in regimen is needed because of treatment failure, an entirely new second-line regimen will have to be used, with the second-line regimen including at least one drug from a new therapeutic class. This type of regimen is recommended so that the likelihood of treatment success may be increased and the risk of resistance minimised.
48. In order to prescribe the most appropriate drug regimen, it is necessary to have regard to the need to minimise potential antagonism between specific drugs and additive side effects, maximise antiviral potency, and maintain future treatment options.
49. There are also particular constraints applicable to particular patient groups, which limit the range of treatment options. I will give some examples of these.

Pregnant women and women of child-bearing potential

50. The choice of ARV medicines available to pregnant women and women of child-bearing potential is restricted. The regimen must be based on a consideration of the possibility that HAART may be received prior to the detection of pregnancy and during the first trimester including the period of foetal organ development.

Children

51. Not all available ARV medicines are suitable for children. While many are available in child-specific formulations (including dosages based on weight or body surface area), some PIs are not recommended due to a lack of suitable paediatric drug formulations.

People with TB and HIV co-infection

52. In patients who qualify for HAART and where there is a high risk of HIV disease progression or death during the period of the TB treatment, HAART should be started concurrently with TB therapy. Otherwise, it can be postponed for the first two months of TB therapy.

Presence of other medical conditions

53. Some medical conditions are relative contra-indications to the prescription of specific ARV medicines. For example:

- a) Peripheral neuropathy is a degenerative condition of the sensory nerves to the limb extremities, which manifests as pain and numbness in the hands and feet. The ARV medicine d4T may exacerbate the symptoms of peripheral neuropathy.
- b) Previous inflammation of the pancreas, a cause of severe abdominal pain, may be reactivated by use of ddI.
- c) Pre-existing inflammation of the liver (hepatitis) may increase the incidence of NVP liver damage.
- d) Existing renal dysfunction may be contra-indicated for TDF.

54. The result is that even with the number of drugs presently available, these constraints limit the ability to develop optimised regimens for all patients.

55. This illustrates the need for a wide choice of ARVs, so as to be able to match a specific regimen for the many clinical situations which occur in HIV infection.

Substitutability of ARV medicines

56. The nature of HAART, coupled with the narrowing of choices in respect of pregnant women and women of childbearing potential, children and people with TB and other medical conditions means that ARV medicines, even within the same therapeutic class, cannot be considered as fully substitutable for each other.

57. Because of the matrix of interconnected factors relating to toxicity and effectiveness of treatment, access to a wide choice of ARV medicines is required in order to effectively administer HAART.

Treatment interruption and its implications

58. I have been asked to explain the individual and public health implications if the drug which is the subject of this complaint were no longer available in South Africa, or if sufficient supplies of this drug were not available – in other words, if EFV were no longer available for a short or long period for whatever reason. I would like to point out that my comments are made within the context of the large number of public sector patients who are already on an EFV-based regimen.

- a) EFV is regarded as an extremely important drug in its class as it has one of the longest half lives, meaning that it needs less dosing – in other words it is taken once daily.
- b) Drug resistance among patients may occur if no alternative regimen were immediately available.
- c) Where NVP is used as a replacement for EFV, increased liver function monitoring would be necessary.
- d) Where a patient has had a previous severe reaction to NVP, then switching the patient back to NVP can be fatally dangerous for him or her.
- e) While the possibility of high rates of toxicity in all patients may be regarded as theoretical, there is evidence that there is more toxicity to NVP in patients with a higher CD4 count when initiating ART. While it is still unclear whether this is the same for those patients who need to swap regimens, it is a monitoring concern for clinicians such as me.
- f) Where a patient is on EFV and also on TB drugs, particularly rifampicin, and EFV is no longer available for whatever reason, one alternative would be to switch the patient to NVP.
- g) This is complicated by an increased rate of hepatotoxicity and lowering of NVP levels in the blood.

- h) Another alternative would be for patients on rifampicin to be given LPV/r, but this is complicated by complex interactions with liver metabolism requiring additional doses of RTV or LPV/r. There is an increased risk of hepatotoxicity with these regimens.

59. For these reasons, in my considered expert opinion, if EFV were not available to health care workers for the treatment of patients, it would have serious public health consequences.

60. I should also point out that unintended consequences of interrupted treatment, irrespective of the regimen are:

- a) An undermining of adherence messages and patient confidence in the health care system (why should patients be adherent when the health system is unable to provide a sustainable supply of medicines?); and
- b) An increased risk of AIDS and death, especially in those patients who had very low CD4 counts at treatment initiation, where treatment interruption is for a significant duration of time.

Adherence

61. Adherence to ARV treatment is essential to maintain long-term health benefits and avoid the development of drug resistance.

62. This is also recognised by the national *HIV & AIDS and STI Strategic Plan for South Africa, 2007–2011* (NSP), which states that “the complexity of maintaining more than one million people on antiretroviral therapy at high levels of adherence will emerge as a key medium term challenge and will require systems and resources. This underscores the critical need to ensure that investments in treatment build the capacity of the health system more generally and also contribute to strengthening prevention” (at page 22).

63. In my extensive years of working in the area of HIV/AIDS, I have found that simplified drug regimens contribute to increased patient adherence to HAART.

64. If pills are packaged together, this makes it easier for patients not to lose some of them. If all ARV medicines that patients need are combined into one pill, it is easier and more convenient for patients to adhere to their treatment regimen. For patients such as children, health care workers, miners, and workers in the security industry who work shifts, it would be ideal if they were only to take one pill daily.
65. The goal of having FDCs or co-packaged ARV products is to simplify regimens to allow for easier distribution and improved patient adherence, particularly in resource poor settings. Ideally, proposed combination products should be relatively well tolerated and easy to administer while providing potency and a sufficient barrier to the emergence of drug resistance.
66. Triple FDCs or co-packaged products are probably most useful for treatment-naive patients – who make up the majority of people of treatment in South Africa at present.
67. The WHO states that regimens can be simplified by –
- a) Reducing the frequency of taking pills by –
 - i. Using products with long-acting active pharmaceutical ingredients (APIs);
 - ii. Developing sustained or extended release versions; or
 - iii. Combining standard strengths of more than one API in an FDC; or
 - b) Co-packaging two or more separate pills in a single blister pack.
68. Two FDCs that contain EFV – TDF/FTC/EFV (to be marketed in South Africa as Atripla™) and TDF/3TC/EFV – have already been developed.
69. Some multinational generic companies, including those that have subsidiaries in South Africa, market the following co-packaged products containing EFV in other countries:

- a) AZT/3TC + EFV;
- b) d4T/3TC + EFV; and
- c) 3TC + ddl + EFV.

70. In my expert clinical view, co-packaged and FDC products are important for adherence because they make it easier for patients, especially children and shift workers, to adhere to daily drug regimens.

Conclusion

71. ARV treatment is a complex area of medicine, particularly since clinicians have limited choices of drugs within therapeutic classes.

72. To deal properly with the proposed increase in patient numbers in South Africa, we need simplified first-line regimens – preferably in the form of a single FDC.

ROBIN WOOD

I CERTIFY THAT THE DEPONENT HAS ACKNOWLEDGED THAT HE KNOWS AND UNDERSTANDS THE CONTENTS OF THIS AFFIDAVIT WHICH WAS SIGNED AND SWORN TO BEFORE ME AT CAPE TOWN ON THIS ___ DAY OF NOVEMBER 2007 AND THAT HE HAS NO OBJECTION TO TAKING THE PRESCRIBED OATH AND CONSIDERS SAME TO BE BINDING ON HIS CONSCIENCE.

COMMISSIONER OF OATHS