Appendix 1: An unanswered submission to the MCC on 6 August 2002 regarding perinatal nevirapine treatment

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 only for use in adults demonstrating clinical and/or immunological deterioration.
9. BI was granted provisional licences subject to similar conditions by the European Medicines Agency (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 TPP due to

'an absence of scientific evidence of efficacy and … concerns about safety'.

11. The TPP 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 a 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 needlestick 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, 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 Miiro 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 La Montagne, 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 La Montagne, 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 La Montagne 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 Miiro's allegation that the missing files are 'stacked up in a container due to the ongoing rehabilitation at the hospital'. La Montagne also made the claim, contradicting both Miiro 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 eighty 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, fifteen per cent parasitic infections, thirteen per cent anaemia and about five 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. On 19 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 article: '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, inter alia, at Kalafong Hospital, Pretoria.

52. La Montagne'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 La Montagne'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 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. La Montagne'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 seventy per cent]. 645 mothers randomised.' In other words, about seventy 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 only tentative.

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 of nevirapine 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 La Montagne'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, and 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 Such 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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