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The effects of anti-HIV nucleoside drugs on the virulence of clinically relevant candida species

Ahmadou, Ahidjo Bintou

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MSc Dissertation Corrections
Title: The Effects of Anti-HIV Nucleoside Drugs on the Virulence of Relevant *Candida* species

Name: B. Ahmadou Ahidjo
Student Number: 0420652W

A. Internal Examiner

Page 1 2nd Paragraph: *Candida* now referred to as a yeast and not a fungus

Page 2 end of last paragraph: The following was added: "In humans however, it appears that cellular factors play a protective role mucocutaneous infection, while humoral factors play a larger role in the prevention of dissemination of Candida infections (Challacombe, 1994)."

Page 11 2nd Paragraph: This was left unchanged, as the antfungal agents were listed in order of development/discovery

Page 12 last line: Figure 1.6 changed to Figure 1.3

Page 13: The figure was not referenced as it was drawn by the candidate.

Page 16: The $\Delta^{(5,6)}$ of sterol $\Delta^{(5,6)}$ desaturase represents the position of the carbon double bonds in the compound

Page 20 2nd Paragraph: The sentence was amended to: "…they found an associated decrease in *Candida* biofilm formation in patients younger than 35 years, as well as patients who had CD_4+ counts of greater than 350 cells/l, and attributed an increase in biofilm formation to the use of zidovudine at the time of sampling (Jin *et al.,* 2003)."

Page 20 last paragraph: The term "government hospitals" was replaced by "State hospitals".

Page 22 Table 1 The following was added: "The second line regimen is given to patients only when toxicity or treatment failure occurs with the first line regimen, and regimen 1b is given to women who can and/or who want to fall pregnant (Simelela, 2004)."

Page 31: The sentence was corrected to: "… just before they started antiretroviral therapy. Patient details were not known to the investigator, and patient consent was obtained before collection of swabs".

Page 33 last paragraph: The sentence was changed to: "One hundred microlitres of each yeast suspension…"

Page 45: The quick-boiling DNA extraction method was the method mostly used as it was quicker, cheaper, and only small quantities of DNA are required for genetic identification by PCR.

Page 50: The sentence was changed to: "A standard colorimetric assay, the CellTiter 96® AQ_{ueous} One Solution Cell Proliferation Assay (Promega), was used as per manufacturer's instructions." This assay was obtained from Promega and the manufacturer's instructions were followed.

Page 52 first Pargraph: The sentence was amended to read: "The NRTIs currently recommended for use in South Africa (Simelela, 2004) are didanosine (ddI), lamivudine (3TC), stavudine (d4T) and zidovudine (AZT)."

Page 57 first Pargraph: The sentence was amended to read "…isolates were not identified as *C. albicans*..."

Page 59 first line: The sentence was amended to read: "After a 3 x 10^7CFU/ml cell suspension of each patient isolate was obtained…"

Page 61 legend: The following was added to the end of the sentence: "(please refer to page **53**)"

Page 67 legend: The candidate opted not to include the significance values as was explained to in the text. However, the following was added to the end of the sentence: "(please refer to page **66**)"

Page 70 Paragraph 2 second sentence: The sentence was left unchanged because different molecules increase the virulence of different organisms. Citing all the molecules that increase the virulence of all pathogenic organisms is just not feasible.

B. External Examiner

Page 10: spelling of echinocandin, allylamines, morpholines and flucytosine corrected

Page 11: Spelling of *Penicillium griseofulvum* corrected

Page 11 3rd Paragraph: No correction was made as amphotericin B is a polyene and not an allylamine nor a phenylmorpholine

Page 14: Spelling of lipophilic correct

Page 19: Comma removed before (Dromer *et al*...)

Page 20: A space was inserted between than and 35 years

Page 20 last paragraph: The last sentence was amended to "Historically amphotericin B was the recommended drug of choice for a variety of fungal infections in HIV/AIDS patients attending state hospitals in South Africa. However, in the last five years, as part of a Diflucan partnership programme with the South African Ministry of Health, Pfizer Inc. has made fluconazole available to state hospitals at no cost. As yet, resistance to fluconazole has not been observed, while an 8.4% resistance to amphotericin B has been reported (Blignaut *et al.*, 2002 (a))."

Page 27: The sentence of the last paragraph was amended to: "Increases in virulence of the organism may well be triggered by such factors, which can contribute to HIV-positive individuals eventually developing oral thrush (Sanchez-Vargas *et al.*, 2005)."

Page 28: Spelling of Steele corrected

Page 29: In the reviewer's comments, this was annotated as **page 27**. The sentence was amended to: "…..since an estimated 5.5 million South Africans are infected with the virus (UNAIDS, 2006

Report on the global AIDS epidemic), and oral candidiasis remains the most prevalent fungal infection (Blignaut *et al.,* 2002)."

Page 33: The sentence was amended to "One hundred microlitres of each yeast suspension…"

Page 37: A space was inserted as suggested

Page 38: This was corrected to 20 800g

Page 48: Spelling of Labotec corrected

Page 51: The section was amended to: "Amphotericin B was diluted in dimethyl sulphoxide (DMSO) to a concentration of 3200µg/ml. This was serially diluted (1/10) to a final concentration of 0.03µg/ml. A 100µl volume of each dilution was inoculated in wells 1-11 of a flat bottom microtitre plate. To each of these dilutions, 100µl of 0.5-2.5 x 10^3 CFU/ml of each yeast isolate was added. A positive control i.e. "yeast with no amphotericin B" was added into well 11 of the microtitre plate, and a negative control i.e. "RPMI with no yeast" was added into well 12.
The plates were then incubated at 36°C ± 1°C for 48hrs, and evaluated visually, by eye, observing the presence or absence of visible growth."

Page 57: The sentence was amended to: **"**It is possible that these were either *C. albicans* isolates that did not have the IS1 genotype (Blignaut *et al.* 2002(b)), or *Candida dubliniesis*…"

Page 74: The sentence was amended to: "In immunocompromised individuals, *Candida* cells proliferate easily because, amongst others, the *Candida*-killing activity of phagocytes is suppressed (Ueta *et al.*, 2001).