

**CHRONIC INFLAMMATORY LUNG DISEASE IN HUMAN IMMUNODEFICIENCY
VIRUS (HIV)-INFECTED CHILDREN. EPIDEMIOLOGICAL CONSIDERATIONS,
AETIOLOGICAL DETERMINANTS AND THE EFFICACY OF LOW DOSE
ERYTHROMYCIN IN BRONCHIECTASIS**

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3. Masekela R, Gongxeka H, Green RJ, Sathekge M. Positron emission tomography in the prediction of inflammation in children with human immunodeficiency virus-related bronchiectasis. *Hell J Nucl Med* 2012;15:23-27.
4. Masekela R, Green RJ. The role of macrolides in childhood non-cystic fibrosis related bronchiectasis. *Mediators Inflamm* 2012;ID134605:1-7.
5. Green RJ, Becker PJ, Labuschagne D, Kitchin OP, Masekela R. Disease progression unrelated to passive environmental tobacco smoke exposure in HIV-infected children. *Int J Collaborative Res Int Med Public Health* 2012;4:130-135.
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In this research, the statistical planning and analyses, and recommendations arising from these analyses, have been done in consultation with Prof PJ Becker of the Institute of Biostatistics of the Medical Research Council of South Africa, as well as Prof P Rheeder of the Clinical Epidemiology Unit of the University of Pretoria.

DECLARATION

This thesis is the candidate's own original work, performed in the Department of Paediatrics and Child Health, University of Pretoria.

R. MASEKELA

ABSTRACT

Human immunodeficiency virus (HIV) infection has reached epidemic proportions in South Africa. The availability of highly active anti-retroviral therapy (HAART) prolongs life in HIV-infected persons, who may subsequently present with chronic manifestations of HIV-infection. The respiratory morbidity attendant to HIV-infection, even in the presence of HAART is high, the aftermath of which is lung tissue destruction and bronchiectasis. As a consequence of the political decision not to offer HAART to HIV-infected children, a number of children in South Africa have been left with severe consequences of uncontrolled HIV-infection. Bronchiectasis is one of those and because children with this devastating condition were numerous in the Pretoria region, the author and her colleagues began a Chronic Lung Disease Clinic in that region. This prompted the idea of investigating both the epidemiological profiles of these children and an attempt to intervene with both standard bronchiectasis guideline care and the use of a form of therapy commonly employed in other forms of bronchiectasis. This thesis explores those ideas.

Important new and novel findings that were consequent were; that bronchiectasis is diagnosed late in HIV-infected children at a mean age of 6.9 years. The predominant organisms cultured from the airways are *Haemophilus influenzae* and *parainfluenzae* in 49% of samples. *Pseudomonas aeruginosa* (PA), common in cystic fibrosis (CF)-bronchiectasis is an uncommon pathogen in HIV-related bronchiectasis; isolated in only 2% of specimens. Tuberculosis (TB), at least as reported, is a significant antecedent of bronchiectasis, reported in 48.5% of children. A further 21.2% of the patients had received more than two courses of anti-TB treatment. However, proof of TB infection has been lacking. Respiratory morbidity is significant with the mean forced expiratory flow in one second (FEV₁) of 53%, in this cohort at the time of presentation. Thirty-six percent of all children were exposed to environmental tobacco smoke, although this was not correlated with disease severity or HIV-disease progression. There is elevation of immunoglobulins in HIV-related bronchiectasis, with a mean IgE of 79 kU/l. This was not, though, associated with HIV disease progression as previously described in adult studies, nor with the presence of allergic bronchopulmonary aspergillosis (ABPA). The elevation in IgE

was also not associated with an elevation of T helper-2 mediated cytokines, confirming the lack of association with atopy.

The predominant cytokine, identified is interleukin (IL)-8, both systemically and locally (in airway secretions). There was elevation of other T helper-1 driven cytokines, reflecting an ability to mediate adequate inflammatory responses, which was independent of the level of immunosuppression. With the presence of HAART, there was a decline in the pro-inflammatory cytokines over time, which may be attributed to the ongoing effect of HAART that ties in to, or goes beyond the restoration of T cell numbers.

Soluble triggering receptor expressed on myeloid cells (sTREM), an innate immune marker, is elevated in children with HIV-related bronchiectasis when compared to a control group of children with cystic fibrosis-related bronchiectasis. sTREM is not associated with the presence of exacerbations and the level of immunosuppression. The use of an anti-inflammatory drug erythromycin also did not impact the sTREM values. There was also no relationship between sTREM and pro and anti-inflammatory cytokines and chemokines.

Fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) could not reliably predict the presence of pulmonary exacerbations. Its diagnostic value was limited to identifying disease activity in acute pneumonia. ^{18}F -FDG PET also had no significant correlation with CRP, inflammatory cytokines or markers of HIV disease activity.

In a randomised controlled trial of erythromycin, a cost-effective immunomodulatory drug, compared to placebo, erythromycin was ineffective in reducing the number of pulmonary exacerbations. Erythromycin also failed to demonstrate any effect on systemic and local pro- and anti-inflammatory cytokines/chemokines. With access to anti-retroviral therapy, airway clearance, nutritional rehabilitation and vigilant follow

up there was an improvement in pulmonary function parameters and stability of the degree of bronchiectasis that we propose is probably in keeping with an organ system disease modifying effect that may be, an as yet, undefined and undescribed byproduct of HAART.

Keywords

Paediatrics

Microorganisms

Biomass fuels

Highly active antiretroviral therapy

Atopy

Positron emission tomography

Macrolides

Cytokines

Chemokines

Soluble triggering receptor expressed on myeloid cells.

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DEDICATION

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