**Abstract:** A general non-specific marker of disease activity that could alert the clinician and prompt further investigation would be of value in patients with HIV/AIDS, especially in resource limited environments.

**Introduction**

In the present study the suitability of neopterin as a potential non-specific marker of disease activity is examined. Neopterin, a catabolic product of the purine nucleotide guanosine triphosphate, is produced from guanosine 5'-triphosphate (GTP) that is cleaved by guanosine nucleotide guanosine triphosphate, is produced from guanosine 5'-triphosphate (GTP) that is cleaved by guanosine triphosphate (GTP)-cyclohydrolase 1 is stimulated, predominantly, by T-helper cell type-1 derived interferon-γ but co-stimulation by tumour necrosis factor alpha may contribute. The value of neopterin as a non-specific indicator was examined in terms of its potential as indicator of inflammatory status, as indicator of immune deficiency or dysfunction, the effects of anti-retroviral treatment and as indicator of TB co-infection. In these assessments the efficacy of neopterin was validated by comparison with immune-related factors such as the acute phase protein C-reactive protein (CRP), CD4 counts, as well as pro- and anti-inflammatory cytokines. In addition, neopterin levels were compared to that of a number of factors routinely measured for diagnostic purposes and elsewhere described as biomarkers.

**Methods**

**Study population and ethics statement**

This was a cross-sectional, non-intervention study comprising of 105 HIV positive adult patients recruited from the Kafafong secondary hospital in Pretoria, South Africa, and a control group of 60 donors from the South African National Blood Service who tested HIV negative and were therefore considered HIV uninfected. A total of 75 patients were on antiretroviral therapy (HAART) group and 30 patients were HAART-naïve. Ethical clearance, in accordance with the declaration of Helsinki, the National Health Act and the policy of the University, was received from the Faculty of Health Sciences Research and Ethics Committee of the University of Pretoria (Number: 107/2008). The committee also approved the documentation used for obtaining either written or verbal voluntary informed consent prior to the study. Participants who could not read or write were informed by a clinician about the nature and purpose of the study before verbal consent was obtained. Verbal consent was documented under the relevant section on the consent form which was acknowledged and signed by the clinician and investigator.

**Cytokine and neopterin assays**

Plasma neopterin was measured by commercial enzyme linked immune-absorbent assay (Immuno-Biological Laboratories Inc., USA). The cytokines IL-2, IL-4, IL-6, IL-10, TNF and IFN-γ were measured in plasma by cytomeric bead array (CBA) kit protocol (BD Biosciences, San Jose, CA, USA) using flow cytometry. The CBA cytokines were analysed on a FACS Array Bioanalyzer using FCAP FC5 Filter and FCAP Array software (BD Biosciences, USA). Routine blood variables were analysed by the National Health Laboratory Service (NHLS) at Kafafong.

**Statistical analyses**

The data was first tested for normality, followed by log transformation as the raw data was not normally distributed. Transformed data were analysed using one way analysis of variance (ANOVA) for comparison between groups. Pairwise comparisons were undertaken by Tukey HSD and Scheffe methods. Spearman rank correlations were computed to determine associations between variable groups. Area under the ROC curve (AUROC) values were determined using logistic regression and CD4 cut-offs of less than 200 cells/µl. Analyses were performed at a significance level of p<0.05 using STATA statistical analysis software (version 12.1).

**Results**

The suitability of neopterin as a general non-specific marker of disease activity in HIV/AIDS patients was examined in a group of 105 HIV/AIDS (HIV-1) patients with a mean viral load of 2.75 ± 1.36 log10 copies/ml and a CD4 count of 257.97 ± 193.06 cells/µl. The demographic information of the study subjects can be seen in Table 1.

| Table 1 Demographic information for the patient and control groups |
|---------------------------------|-----------------|-----------------|-----------------|
|                               | HAART            | HAART-naïve     | Controls        |
| n                               | 75               | 30              | 60              |
| Females                         | 48 (64%)         | 18 (60%)        | 38 (63%)        |
| Age (years)                     | 37.86±8.86       | 37.13±10.24     | 31.81±8.09      |
| BMI (kg/m²)                     | 23.83±6.31       | 20.96±3.62      | 21.96±4.81      |
| Average months on HAART         | 15.86±16.49      | -               | -               |
| TB co-infection at baseline     | 14 (19%)         | 10 (33%)        | -               |

**CRP, cytokines and CD4 counts were employed in the appraisal of neopterin as non-specific biomarker of the inflammatory status, immune deficiency, the effects of anti-retroviral treatment and TB co-infection. The cytokines included the pro-inflammatory cytokines IL-2, IL-6, TNF and IFN-γ as well as the anti-inflammatory cytokines IL-4 and IL-10. A comparison between the total patient group, the group on HAART, the HAART-naïve and the control group levels of immunological factors can be seen in Table 2.**
The validity of neopterin as indicator of immune deficiency was tested against CD4 counts, CRP and cytokine levels. The results can be seen in Table 3.

The power of discrimination, in terms of area under the ROC curve (AUROC), of neopterin, CRP and IL-6 was also tested for the total patient group in relation to CD4 counts of less than 200 using logistic regression. The discriminatory power of neopterin (AUROC = 0.803) was found to be higher than that for CRP (AUROC = 0.658), and for IL-6 (AUROC = 0.753).

Table 2 Comparison of immunological and other variables between the controls and patient groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Total Patients</th>
<th>HAART</th>
<th>HAART-Naive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 (pg/ml)</td>
<td>9.14±2.26</td>
<td>20.06±8.31</td>
<td>18.95±8.41</td>
<td>22.74±7.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-4 (pg/ml)</td>
<td>8.07±0.92</td>
<td>11.96±0.1</td>
<td>11.65±0.16</td>
<td>12.70±3.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>0.69±1.62</td>
<td>11.16±1.95</td>
<td>9.56±12.54</td>
<td>15.04±19.34</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>1.45±1.32</td>
<td>16.41±12.53</td>
<td>12.44±12.38</td>
<td>19.82±11.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TNF (pg/ml)</td>
<td>1.71±1.7</td>
<td>5.74±6.38</td>
<td>5.65±8.39</td>
<td>5.95±3.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IFN-γ (pg/ml)</td>
<td>24.85±8.96</td>
<td>44.00±22.55</td>
<td>41.43±14.14</td>
<td>53.68±34.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NPT (nmol/l)</td>
<td>8.23±5.71</td>
<td>45.57±14.82</td>
<td>34.51±35.70</td>
<td>66.63±40.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NPT/IL-6</td>
<td>0.34±0.75</td>
<td>3.81±3.74</td>
<td>3.04±3.34</td>
<td>5.63±4.05</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-2/IL-6</td>
<td>1.15±0.26</td>
<td>1.68±0.76</td>
<td>1.39±0.64</td>
<td>1.96±0.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6/L-6</td>
<td>0.06±0.14</td>
<td>0.86±1.17</td>
<td>0.74±1.05</td>
<td>1.16±1.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IFN-γ/IL-6</td>
<td>3.25±1.02</td>
<td>3.97±3.01</td>
<td>3.59±1.26</td>
<td>4.87±5.12</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>25.93±11.23</td>
<td>22.88±36.13</td>
<td>34.08±75.78</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 cells/μl</td>
<td>257.97±193.06</td>
<td>296.21±195.50</td>
<td>170.05±162.76</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VL (log10 copies/ml)</td>
<td>2.75±1.36</td>
<td>2.48±1.12</td>
<td>3.57±1.71</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>33.40±7.55</td>
<td>34.94±6.67</td>
<td>29.50±8.37</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A/G ratio</td>
<td>0.68±0.25</td>
<td>0.73±0.24</td>
<td>0.53±0.21</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.83±2.36</td>
<td>12.16±2.36</td>
<td>10.97±2.05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>17.4±5.34</td>
<td>17.52±5.40</td>
<td>17.24±4.02</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Data expressed as mean±SD; IL = interleukin; TNF = tumour necrosis factor; IFN = interferon; NPT = neopterin; VL = HIV viral load; A/G = albumin to globulin ratio; RDW = red cell distribution width
*p<0.05 for HAART vs. HAART-naive

Table 3 Correlations of neopterin with CD4 counts, CRP, IL-6, albumin, A/G ratio, haemoglobin and red cell distribution width

<table>
<thead>
<tr>
<th>Neopterin with</th>
<th>Total Patients</th>
<th>HAART</th>
<th>HAART-Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rho p-value</td>
<td>Rho p-value</td>
<td>Rho p-value</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>-0.48 ± 0.0001</td>
<td>-0.43</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.37</td>
<td>0.0010</td>
<td>0.490</td>
</tr>
<tr>
<td>CRP</td>
<td>0.355</td>
<td>0.0006</td>
<td>0.610</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>0.301</td>
<td>0.0024</td>
<td>0.277</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.547</td>
<td>0.0001</td>
<td>-0.447</td>
</tr>
<tr>
<td>A/G ratio</td>
<td>0.469</td>
<td>0.00001</td>
<td>0.423</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>-0.597</td>
<td>0.00001</td>
<td>-0.555</td>
</tr>
<tr>
<td>RDW</td>
<td>0.342</td>
<td>0.001</td>
<td>0.472</td>
</tr>
</tbody>
</table>

*Spearman Rho rank correlation statistically significant, p<0.05. IL = interleukin; CRP = C-reactive protein; IFN = interferon; A/G ratio = albumin/globulin ratio; RDW = red cell distribution width

Logistic regression results in a comparison between neopterin, albumin, the AG ratio, haemoglobin and RDW as indicators of immune deficiency were: neopterin (AUROC = 0.978), albumin (AUROC = 0.987), the A/G ratio (AUROC = 0.950), haemoglobin (AUROC = 0.334) and RDW (AUROC = 0.589). The value of neopterin as a biomarker in HIV/AIDS was previously described as having tuberculosis (TB) co-infection (spu-
However, although higher pro-inflammatory activity was confirmed in the patients, higher anti control levels (p<0.05) were, as reported elsewhere, also seen in the levels of the anti-inflammatory cytokines (Table 2). Nevertheless, when the pro- versus anti-inflammatory activity was investigated it was found that the ratio neopterin/IL-4 was indeed higher in the HAART naïve (p=0.001), as well as in the HAART patients (p=0.02), than in the controls. This imbalance with a shift towards inflammation in HIV/AIDS was confirmed by the ratios of the individual pro-inflammatory cytokines to that of the anti-inflammatory cytokine IL-4. Significantly higher than control ratios were seen for IL-2/IL4 (HAART: p=0.001; HAART-naïve: p=0.0007), IL-6/IL4 (HAART: p=0.001; HAART-naïve: p=0.0065), as well as for INF/IL4 (HAART: p=0.019; HAART naïve: p=0.009).

Pro-inflammatory dominance with cell-mediated immunity in ascendency was thus shown in the group on anti-retroviral therapy, as well as in the group not yet on anti-retroviral therapy. Such inflammatory activity, demonstrated here by neopterin levels and confirmed by cytokine results, is implicated in the pathogenesis of HIV/AIDS.

Effect of HAART on the pro-inflammatory/anti-inflammatory (cellular/humoral immune) status

The mean IL-6 level in the HAART group was 48% lower (p=0.0001) than that of the HAART naïve group, the mean IL-6 level was 43% lower (p=0.01), the mean IFN-γ was 22.8% lower (p=0.017), the mean IL-2 was 16.7% lower (p=0.076) and the CRP level, although not statistically significant, was 33% lower. However, the HAART group still showed significantly higher inflammatory activity than the control group. In contrast, the levels of the anti-inflammatory cytokine, IL-4, were not significantly different between the HAART and HAART naïve groups (Table 2). These results supported the notion of neopterin as the better marker of inflammatory activity and are in agreement with the concept of advanced HIV/AIDS as a condition with increased inflammatory activity.

As an imbalance between pro- and anti-inflammatory activity, in favour of pro-inflammatory, has previously been implicated in the pathogenesis of HIV/AIDS, it was of interest to see to what extent this imbalance was corrected by antiretroviral treatment. The ratio between neopterin and the main anti-inflammatory cytokine IL-4 for HAART was significantly lower (p=0.002) than that for the HAART naïve patients — pointing to suppression of cellular (pro-inflammatory) relative to humoral (anti-inflammatory) activity by antiretroviral treatment. However, the ratio in the HAART group was still higher (p=0.02) than in the control group, confirming the persistence of a shift towards pro-inflammatory activity despite antiretroviral treatment. The ratios of the individual pro-inflammatory cytokines to the level of the anti-inflammatory cytokine IL-4 (IL-2/IL4, IL-6/IL4, IFN-γ /IL-4) were also lower in the HAART than in the HAART naïve group, none were significantly lower.

This persistent, albeit downgraded, presence of inflammation, and imbalance between pro- and anti-inflammatory activity, despite effective antiretroviral therapy, has previously been reported and is described as a major contributor to the pathogenesis of HIV/AIDS.

Neopterin as indicator of immune deficiency

Neopterin has previously been shown as a measure of the degree of immune deficiency in HIV/AIDS patients. In the present study the potential of neopterin as indicator of immune deficiency was again investigated by comparing neopterin levels to that of CD4 counts. Results with neopterin were then compared to that with CRP and cytokines. Negative correlations were found between neopterin and CD4 counts for the total patient group (r=-0.484, p=0.0001), the HAART group (r=-0.43, p=0.001) and the HAART-naïve group (r=-0.503, p=0.002) (Table 3). 93.3% of the HAART naïve patients and 73.3% of the HAART patients had higher than normal neopterin levels. These results, which suggest neopterin as an indicator of immune deficiency, are in line with that of previous publications.

Neopterin was subsequently compared to CRP and cytokines as immune deficiency indicators. CRP and one of the cytokines investigated, that is, IL-6, showed significant negative correlations with CD4 counts for the total patient group (CRP: r=-0.328, p=0.0007; IL-6: r=-0.431, p=0.0001) and the HAART group (CRP: r=-0.410, p=0.005; IL-6: r=-0.553, p=0.009), but not for the HAART naïve group (Table 4). In contrast to neopterin, only 49.3% of the HAART naïve patients and 46.7% of the HAART patients had higher than normal CRP reference levels. 83.3% of the HAART naïve patients and 65.3% of the HAART patients had higher than normal IL-6 levels.

Logistic regression showed the discriminatory power of neopterin (AUROC = 0.803) to be higher than that for CRP (AUROC = 0.658), and for IL-6 (AUROC = 0.753). Neopterin was therefore shown to be superior to CRP and to individual cytokines as indicator of immune deficiency.

Neopterin and HIV/AIDS with TB-co infection

Neopterin levels are known to be significantly higher than that of the control group for CRP and to individual cytokines as indicator of immune deficiency. Neopterin was subsequently compared to CRP and cytokines as immune deficiency indicators. CRP and one of the cytokines investigated, that is, IL-6, showed significant negative correlations with CD4 counts for the total patient group (CRP: r=-0.328, p=0.0007; IL-6: r=-0.431, p=0.0001) and the HAART group (CRP: r=-0.410, p=0.005; IL-6: r=-0.553, p=0.009), but not for the HAART naïve group (Table 4). In contrast to neopterin, only 49.3% of the HAART naïve patients and 46.7% of the HAART patients had higher than normal CRP reference levels. 83.3% of the HAART naïve patients and 65.3% of the HAART patients had higher than normal IL-6 levels.

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Comparison of neopterin levels to that of circulating substances and ratios elsewhere described as biomarkers in HIV/AIDS patients

Locally produced cytokines could bind to their target tissues or be neutralized by soluble receptors. Cytokine release may therefore not be accurately reflected by circulating levels. The circulating level of neopterin, on the other hand, is largely a product of the balance between synthesis and renal excretion. It therefore be of diagnostic/prognostic value in TB and others not be substituted by the results of the present study. In contrast to our expectations that the balance between pro- and anti-inflammatory activity would be more unmanageable with TB-co-infection, the difference for the neopterin/IL-4 ratio between patients with and without TB co-infection (p=0.059) was non-significant when judged at a 0.05 level of significance.

Advantage of neopterin above that of the measurement of individual cytokines

Previous indications that cytokines such as IFN-γ, TNF-alpha, IL-6, IL-10 and the IFN/IL-10 ratio may be of diagnostic/prognostic value in TB and others were not substantiated by the results of the present study.

Nefopterin as indicator of immune deficiency

Neopterin has previously been shown as a measure of the degree of immune deficiency in HIV/AIDS patients. In the present study the potential of neopterin as indicator of immune deficiency was again investigated by comparing neopterin levels to that of CD4 counts. Results with neopterin were then compared to that with CRP and cytokines. Negative correlations were found between neopterin and CD4 counts for the total patient group (r=-0.484, p=0.0001), the HAART group (r=-0.43, p=0.001) and the HAART-naïve group (r=-0.503, p=0.002) (Table 3). 93.3% of the HAART naïve patients and 73.3% of the HAART patients had higher than normal neopterin levels. These results, which suggest neopterin as an indicator of immune deficiency, are in line with that of previous publications.

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Neopterin and HIV/AIDS with TB-co infection

Neopterin levels are known to be significantly higher in individuals with active tuberculosis than in patients with inactive tuberculosis or controls. It would thus seem feasible to expect that HIV/AIDS patients with TB-co-infection would have higher levels of neopterin than HIV patients without TB-co-infection. The ability of neopterin to discriminate between HIV patients with and without active TB was therefore investigated and compared to that of CRP and cytokines.

Neopterin as indicator of immune deficiency

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It is known that the levels of albumin, A/G ratios, haemoglobin and RDW are all adversely influenced by inflammation. With chronic inflammation the levels of albumin, a negative acute-phase protein, decreases as a result of lower synthesis, an increase in fractional metabolic rate, appetite suppression and through an increase in microvascular leakage33,34. Chronic inflammatory conditions can influence haemoglobin levels, RDW and other red blood cell parameters in various ways, most notably processes involved in the anaemia of chronic disease35. The association between RDW and inflammation is so strong that RDW has been described as indicative of inflammation36.

In the present study negative correlations between neopterin and albumin concentrations were observed for the total patient group (r=−0.547, p=0.00001), the group on HAART (r=−0.447, p=0.0002) and the HAART-naïve group (r=−0.475, p=0.014). As for albumin, the A/G ratio declined with increases in neopterin as seen in the negative correlations for the total patient group (r=−0.485, p=0.00001), the HAART group (r=−0.423, p=0.0004) and the HAART-naïve group (r=−0.373, p=0.061). Negative correlation were also found between the haemoglobin and neopterin levels for the total patient group (r=−0.491, p=0.00001) and the group on HAART (r=−0.497, p=0.0004). Positive correlations were also found between the A/G ratio and the CD4 counts for the total patient group (r=0.486, p=0.00001) and the group on HAART (r=0.505, p=0.0003). Haemoglobin concentration correlated positively with the CD4 count for the total patient group (r=0.42, p=0.0003) and for the HAART group (r=0.392, p=0.004). RDW correlated negatively with the CD4 count for the total patient group (r=−0.37, p=0.010) and the group on HAART (r=−0.47, p=0.0004).

Although albumin, the A/G ratio, haemoglobin and RDW were seen to have a positive association with the degree of immune deficiency, neopterin (AUROC = 0.803) was shown to be a better indicator of immune deficiency than albumin (AUROC = 0.487), the A/G ratio (AUROC = 0.504), haemoglobin (AUROC = 0.334) and the RDW (AUROC = 0.589).

Additional reasons why neopterin could be a good non-specific biomarker in HIV/AIDS patients

In addition to evidence of neopterin as a good non-specific marker of disease, as shown in our study, various other phenomena support this assumption. The value of neopterin as indicator of disease progression in HIV has been shown by several laboratories16, and in an earlier paper on HIV/AIDS patients of African ethnicity we showed neopterin to be superior to CRP and procalcitonin as indicator of disease progression37. Another connection between neopterin levels and disease is suggested by the correlation between neopterin and IFN-γ (Table 3). IFN-γ is the major factor responsible for a shift in tryptophan metabolism towards the kynurenine pathway38. Abnormalities in tryptophan metabolism can have a widespread influence on both physical and psychological well-being. In the present study significant positive correlations were found between neopterin levels and the levels of IFN-γ (total patient group: r=0.301, p=0.002; HAART: r=0.277, p=0.017). A further potential link between neopterin levels and disease activity in HIV/AIDS lies in the production of reactive oxygen species (ROS). Excessive ROS is known to contribute to the pathogenesis of HIV/AIDS and corelations have been shown to exist between neopterin levels, increased production of ROS and decreased circulating antioxidants40,41. Other associations, not to be discussed here exist, such as that between neopterin and inactivation of the expression of the proto-oncogene c-fos42, the nuclear factor-xb43, and the INOS gene44. However, the primary association is probably that between neopterin and inflammation.

Conclusions

This study in HIV/AIDS patients showed neopterin to be a better indicator of the inflammatory status, immune deficiency, TB-co-infection and the effects of HAART than CRP or cytokines. Changes in plasma neopterin levels as an indication of the efficacy of HAART or of patient compliance, should be investigated further. In line with the effects of inflammation on various systems, neopterin levels reflect the negative effects of the disease on levels of albumin, haemoglobin, the albumin/globulin ratio and the red cell distribution width.

It is our contention that neopterin levels represent a good non-specific indicator, not only of inflammatory activity, but of the general health status. This statement is made in view of its associations with inflammation, the effects of HAART, immune deficiency, TB-co-infection, the levels of several plasma proteins and, as previously reported, disease progression. The statement is further supported by previously supported diagnostic and prognostic associations between plasma neopterin levels and disorders other than HIV/AIDS. These include viral, intracellular bacterial and parasitic infections, burns, cancer, cardiovascular disease, neurodegeneration, graft versus host disease, autoimmune disorders and a variety of oral afflictions45. However, in view of the effect of inflammation on all physiological systems, the primary importance of neopterin probably lies in its reflection of the degree of inflammation, a major contributor to the pathogenesis of HIV/AIDS and a process involved in a wide variety of pathological processes. The skills required for the analysis of neopterin fall within that of most trained laboratory analysts and the costs are below that of the more specialized techniques. Neopterin therefore offers a relatively inexpensive non-specific biomarker in resource limited environments to alert the clinician to investigate further.

Conflict of interest

None

Acknowledgements:

We thank the staff and patients of the immunology clinic at Kalafong Hospital in Pretoria, South Africa. We also thank the volunteers and staff of the South African National Blood Service at the Pretoria West satellite site. This research was supported by grant funding received from the Medical Research Council of South Africa and the South African Sugar Association.

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