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Early Structural and Functional Changes of the Vasculature in HIV-Infected Children
Impact of Disease and Antiretroviral Therapy

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Background—Premature cardiovascular disease is increasingly recognized in HIV-infected patients, but the mechanisms involved are unclear. The purpose of this study was to determine the impact of HIV infection and antiretroviral therapy (ART) on markers of early vascular disease in children.

Methods and Results—We studied 83 HIV-infected children (56 had taken ART, of whom 31 received a regimen containing protease inhibitors [PIs]; 27 were never treated) and a control group of 59 healthy children. Carotid intima-media thickness (IMT) and brachial artery flow-mediated dilatation (FMD) were measured. IMT was significantly greater in HIV-infected children compared with the control subjects (P<0.001). Among the HIV-infected children, age and treatment were significantly associated with increased IMT. Children exposed to PIs had greater IMT compared with both non–PI-treated children and untreated children (P=0.02). FMD was also significantly reduced in the HIV-infected children compared with control subjects (P=0.02). Pairwise comparisons of different treatment exposure groups revealed that FMD was impaired by a mean of 3.6% (95% CI, 1.8 to 5.3; P<0.001) for children exposed to PIs compared with untreated children and by a mean of 1.8% (95% CI, 0.01 to 3.5; P=0.05) compared with non–PI-treated children. HIV-infected children had lipid abnormalities, but they did not account for the observed differences in either FMD or IMT.

Conclusions—HIV infection in childhood is associated with adverse structural and functional vascular changes that are most pronounced in children exposed to PI therapy. Longitudinal studies are required to differentiate the relative impact of HIV disease and ART and to assess the potential for prevention. (Circulation. 2005;112:103-109.)

Key Words: endothelium ■ HIV ■ protease inhibitors

Human immunodeficiency virus (HIV) infection is a major cause of morbidity and mortality worldwide. In developed countries, life expectancy has increased considerably as a result of antiretroviral therapy (ART), and cardiovascular disease has emerged as an important late concern.1,2 Recent studies have shown a 26% increase in myocardial infarction in HIV-infected adults per year exposure to ART and that metabolic abnormalities related to the use of combination therapy may contribute.3–5 Protease inhibitors (PIs), in particular, are associated with dyslipidemia, insulin resistance, and lipodystrophic phenotype, which may be due to hepatic overproduction of VLDL and, to a lesser extent, impaired clearance.5,6 It has been difficult, however, to separate the effects of HIV disease itself, drug treatment, metabolic consequences, or interactions with the exposure to classic risk factors for atherosclerosis.

Although clinical manifestations of atherosclerosis do not typically present until middle and late adulthood, the process of atherogenesis begins earlier.7 Numerous cardiovascular risk factors have been shown to affect both endothelial vascular function and early structural arterial wall changes from the first decade of life.8,9

We therefore studied children who acquired HIV through mother-to-child transmission to examine the potential effect of chronic HIV infection and ART on measures of vascular structure and function. This population provides the opportunity not only to investigate the impact of HIV infection and ART on the vasculature but to do so without the confounding effect of the cumulative risk factor burden present by adulthood.

Methods

Study Population and Design
We studied HIV-infected children attending Great Ormond Street Hospital (GOSH) NHS Trust (London, UK). Children with current...
opportunistic infections or cardiovascular risk factors, including hypertension, diabetes, and renal failure, were excluded. Of the 96 HIV-infected children identified as eligible for the study, 83 agreed to participate. Fifty-nine healthy volunteer children were recruited as control subjects from healthy siblings of the HIV-infected children and children of staff working at the hospital. No formal matching was used in selecting the control children (apart from siblings). None had a current or recent infectious illness, nor were they receiving any medication or vitamin supplementation.

All children had a clinical examination, including blood pressure measurements, blood sampling, anthropometry, and vascular measurements. Details of past clinical and ART history were extracted from the UK Collaborative HIV Pediatric Study (CHIPS) database. The HIV clinic at GOSH does not use rigid criteria for initiating ART. However, ART is usually started for persistently low or declining CD4% counts and/or clinical deterioration. The nature of the ART regime was not based on measures of disease severity. Ethnicity data were obtained from the National Study of HIV in Pregnancy and Childhood (NSHPC).

Institutional Review Board approval was received, and all parents or caregivers and children, when appropriate, gave written informed consent to participate in the study at the time of the visit.

**Anthropometric Measurements**
Weight and height were recorded, and body mass index (BMI; kg/m²) was calculated. Values were converted to age- and sex-adjusted z scores with the use of UK reference curves. Blood pressure was measured as the average of 3 seated readings with an automated oscillometric device (Omron). A pediatric cuff was used when the arm circumference was <25 cm and an adult cuff when the arm circumference was ≥25 cm.

**Blood Sample Analysis**
Nonfasting blood was taken from all children in heparinized tubes, and 1 mL of plasma was stored at −80°C. Lipid levels and inflammatory markers (see below) were measured in all subjects, and markers of disease activity were assessed in the HIV-infected children.

**Markers of HIV Severity and Inflammation**
HIV RNA viral load was measured by branched DNA assay (Chiron Diagnostics) with a lower limit of detection of 50 copies per mL. CD4% was measured by flow cytometry. For viral load and CD4% measurements, the closest measurements (within 3 months before the study visit) were used if available. High-sensitivity C-reactive protein (hsCRP) was analyzed with an in-house ELISA method.

**Lipoprotein Parameters**
Total cholesterol was measured by enzymatic colorimetry; HDL was measured directly in plasma after precipitation with polyethylene glycol (Roche Diagnostics). Apolipoprotein B (apoB) and lipoprotein (a) [Lp(a)] were measured by immunoturbimetry kits from WAKO and Diasys Diagnostic Systems, respectively. LDL levels and inflammatory markers (see below) were measured in all subjects, and markers of disease activity were assessed in the HIV-infected children.

**IMT Study**
The right and left common carotid arteries were scanned with a 5- to 10-MHz linear-array transducer (Acuson). The carotid bulb was identified, and longitudinal 2D ultrasonographic images of the common carotid artery 1 to 2 cm proximal to the carotid bulb were obtained. The optimal longitudinal image was acquired on the R wave of the ECG and continuously recorded on videotape for 5 seconds. Measurements of the posterior wall of the artery were made from stored images with electronic calipers. IMT was calculated as the distance between the first bright line (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface). Six measurements, the 3 maximum measurements of the right common carotid artery in 3 different frames and the 3 maximum measurements of the left common carotid artery in 3 different frames, were averaged.

**FMD Study**
Each child underwent measurement of endothelium-dependent vascular responses of the right brachial artery by high-resolution ultrasound imaging with an Acuson 5- to 10-MHz linear probe as previously reported. Brachial artery diameter was measured offline by an automatic edge detection system (Brachial Tools) and expressed as a percentage change from baseline diameter. Doppler-derived flow measurements (using a pulsed-wave Doppler signal at a 70° angle) were also obtained continuously. The increase in blood flow after the release of the cuff was expressed as a percentage change from the baseline flow. Endothelium-independent response to glycerol trinitrate (GTN) was also calculated as a percentage change from the baseline diameter after sublingual administration of 25 μg GTN in the HIV-infected children only.

**Statistical Analysis**
In descriptive analyses, parametric summary statistics and significance tests were used when the data were approximately normally distributed; otherwise, nonparametric methods were used. All FMD and GTN analyses were adjusted for baseline diameter; GTN analyses were adjusted for weight. Multivariable regression analysis was used to examine relationships between vascular measurements and HIV infection status and ART exposure with adjustment for potential confounders. Confounders included age, sex, ethnicity, Centers for Disease Control (CDC) stage, hsCRP, glucose, and selected lipid parameters. Variables that were not normally distributed were log_{10} transformed to reduce the influence of outlying observations.

**Results**

**Study Population**
The 83 HIV-infected children had a mean age of 11.0 years (range, 5.4 to 17.7 years); 70% were black; and all had acquired HIV from mother-to-child transmission. The control children were 1 year older than the HIV-infected children; 80% were white and had similar age-adjusted BMI scores (Table 1).

Twenty-seven HIV-infected children had never received ART. The remaining 56 children had taken ART for a median of 5 years (range, 0.2 to 14 years). Of these 56, 31 had received regimens containing a PI (Table 2). At the time of the study, 48 children were taking ART (23 including a PI), and 35 children were not receiving any ART. Of the 31 PI-exposed children, 8 were on combination therapy that did not include a PI at the time of the study visit (median duration since a PI was taken, 1.3 years; range, 0.5 to 2.8 years). Twenty HIV-infected children (24%) had previously experienced a CDC stage C disease; all 20 had been treated with ART (15 exposed to PI therapy) (Table 2).

**Lipoprotein Parameters**
Triglycerides, non-HDL cholesterol, apoB, and Lp(a) were significantly higher in HIV-infected children compared with control subjects. In addition, HIV-infected children had
significantly lower HDL cholesterol levels and mean and peak LDL particle sizes (Table 1).

Within the HIV cohort, differences in lipid parameters were observed between those receiving different treatment regimens (Table 2). Total cholesterol was higher in children receiving ART (both with and without PI) compared with untreated HIV-infected children. Lp(a), apoB, and triglyceride levels were higher in PI-treated children compared with non–PI-treated and untreated HIV-infected children. HDL cholesterol levels were lower in the untreated HIV-infected children compared with treated children, and the latter had levels similar to those in the control children.

**CRP Measurement**

hsCRP was significantly higher in the HIV-infected children compared with control subjects (Table 1). Eight HIV-infected children had markedly increased hsCRP values (CRP >10 mg/L); although they did not have clinical evidence of acute infection, these CRP levels are compatible with acute inflammation. However, the difference in CRP values between control subjects and HIV-infected children remained when the analysis was performed with these 8 children omitted.

**Vascular Measurements**

**IMT Assessment**

IMT measurements were available for 77 of the 83 HIV-infected children and 45 of the 53 control subjects. IMT was higher in the HIV-infected children compared with the control subjects ($P<0.0001$; Table 1) in both unadjusted and adjusted analyses. There was a significant association between IMT and age in the HIV-infected children that was not observed in the control subjects (Figure 1A); for every year increase in age, IMT was increased on average by 0.005 mm (95% CI, 0.0003 to 0.01). There was no association between ethnicity and IMT in either HIV-infected or control children.

There was evidence of a treatment effect when the HIV-infected children were categorized as ever exposed to PIs, non–PI-treated, and untreated ($P=0.03$; Table 2). Exposure to PIs was associated with a higher mean IMT compared with both those untreated ($P=0.04$) and the non–PI-treated group ($P=0.01$; Figure 1B). Similar results were found when the children were categorized according to their treatment regimen at the time of the test (data not shown). There was no association between IMT and CD4% or viral load at the time of the study, but more advanced CDC stage was associated
with greater IMT. However, in multivariate analyses, the higher IMT in children with exposure to PIs could not be accounted for by CDC stage or other potential confounders. Notably, there was no association between IMT and duration of PI therapy.

**FMD Assessment**

FMD measurements were available for 82 of the 83 HIV-infected children and 57 of the 59 control children. Resting vessel size, blood flow, and reactive hyperemia were similar in both groups. FMD was lower in the HIV-infected children than in the control subjects after adjustment for baseline diameter ($P=0.02$; Table 1 and Figure 2A). The relationship remained after adjustment for age, sex, and other potential confounders. There was no evidence of an association between age, sex, ethnicity, lipids, and hsCRP in the whole cohort.

Among the HIV-infected children, there were no differences in baseline vessel diameter, baseline flow, or reactive hyperemia in the different treatment groups. FMD was significantly lower in those exposed to PIs compared with non–PI-treated ($P=0.05$) and untreated ($P=0.001$) children. Similar results were obtained when the analysis was performed by current therapy (Figure 2B). The response to GTN was not associated with exposure to ART (Table 2). As for IMT, CDC stage C was associated with lower FMD. FMD was also inversely related to hsCRP, and this relationship remained after the 8 HIV-infected children whose hsCRP was $>/=10$ mg/L were excluded. However, the relationship between FMD and ART exposure remained after adjustment for CDC stage, hsCRP, and other potential confounders in multivariate analysis.

**TABLE 2. Comparison of ART Exposure in HIV-Infected Children**

<table>
<thead>
<tr>
<th></th>
<th>PI Treated (n=31)</th>
<th>Non–PI Treated (n=25)</th>
<th>Untreated (n=27)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>11.1 (3.5)</td>
<td>11.5 (3.0)</td>
<td>10.3 (2.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Male, %</td>
<td>62</td>
<td>44</td>
<td>63</td>
<td>0.72</td>
</tr>
<tr>
<td>Height z score, median (IQR)</td>
<td>$-0.59 (-1.35–0.18)$</td>
<td>$-0.40 (-0.94–0.06)$</td>
<td>$-0.24 (-1.32–0.38)$</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI z score, median (IQR)</td>
<td>$-0.20 (-0.81–0.75)$</td>
<td>$0.04 (-0.93–0.56)$</td>
<td>$0.62 (-0.25–1.19)$</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Clinical parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>103 (10)</td>
<td>103 (8)</td>
<td>106 (10)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>61 (12)</td>
<td>60 (7)</td>
<td>61 (6)</td>
<td>0.90</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79 (11)</td>
<td>79 (12)</td>
<td>83 (15)</td>
<td>0.37</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.4 (0.8)</td>
<td>4.3 (0.6)</td>
<td>4.4 (0.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>hsCRP, median (IQR), mg/L</td>
<td>1.1 (0.2–2.0)</td>
<td>1.2 (0.4–6.7)</td>
<td>0.4 (0.4–2.0)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Clinical parameters related to HIV and ART</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC stage C, %</td>
<td>48</td>
<td>20</td>
<td>0</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>CD4%, median (IQR)</td>
<td>26 (21–34)</td>
<td>26 (14–29)</td>
<td>22 (19–24)</td>
<td>0.18</td>
</tr>
<tr>
<td>HIV RNA, log$_{10}$ copies/mL</td>
<td>2.30 (0.98)</td>
<td>2.68 (1.11)</td>
<td>4.08 (0.70)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Exposure to ART, median (IQR), y</td>
<td>5.3 (4.7–6.8)</td>
<td>3.8 (2.3–6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to PIs, median (IQR), y</td>
<td>4.2 (2.7–5.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipid/blood results</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.6 (0.9)</td>
<td>4.0 (0.8)</td>
<td>3.6 (0.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4 (0.5)</td>
<td>1.3 (0.5)</td>
<td>1.0 (0.3)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mmol/L</td>
<td>3.2 (1.0)</td>
<td>2.7 (0.7)</td>
<td>2.7 (0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>80 (20)</td>
<td>73 (15)</td>
<td>72 (15)</td>
<td>0.13</td>
</tr>
<tr>
<td>Mean particle diameter, nm</td>
<td>28.0 (1.1)</td>
<td>28.3 (0.7)</td>
<td>28.3 (1.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>Peak particle diameter, nm</td>
<td>27.7 (1.2)</td>
<td>27.0 (1.3)</td>
<td>27.8 (1.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Lp(a), median (IQR), mg/dL</td>
<td>50 (38–86)</td>
<td>33 (17–45)</td>
<td>34 (21–63)</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, median (IQR), mmol/L</td>
<td>1.1 (0.8–1.4)</td>
<td>0.9 (0.8–1.2)</td>
<td>0.9 (0.6–1.4)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Vascular measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.62 (0.07)</td>
<td>0.58 (0.06)</td>
<td>0.58 (0.06)</td>
<td>0.03</td>
</tr>
<tr>
<td>FMD, †%</td>
<td>6.3 (5.4)</td>
<td>8.1 (5.9)</td>
<td>9.9 (5.7)</td>
<td>0.0005</td>
</tr>
<tr>
<td>GTN-mediated dilation, ‡%</td>
<td>14.5 (8.4)</td>
<td>14.0 (9.5)</td>
<td>17.2 (8.9)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range. Eight of the PI-treated children were on combination therapy that did not include a PI at the time of the study visit. Eight children in the non-PI group were off all treatment at the time of the study visit. CD4% and HIV RNA: closest measurement within 3 months before the time of the study visit (n=78 for CD4%, n=77 for HIV RNA). There are 4 CDC stages that reflect the extent of HIV disease progression: N signifies no signs or symptoms; A, B, and C, increasingly severe disease; and C, AIDS). Values are given as mean (SD) unless otherwise stated.

*Global probability values are based on ANOVA or the Kruskal-Wallis test when appropriate.

†Adjusted for baseline diameter; estimates given for mean baseline diameter of 2.80 mm.

‡Adjusted for baseline diameter and weight; estimates given for mean baseline diameter of 2.80 mm and mean weight of 36.9 kg.
This study demonstrates that structural and functional changes of the vasculature are already present during childhood in HIV-infected children. These changes were most pronounced in children receiving PIs but were also observed in non–PI-treated and untreated children. Our findings support a role for both HIV infection itself and ART, particularly PIs, in the pathogenesis of early vascular disease, likely to be relevant to future clinical atherosclerosis.

Several studies have raised concerns about the effect of HIV and ART on both progression of atherosclerosis and cardiovascular events in adults.\textsuperscript{4,16} PIs in particular are associated with metabolic abnormalities and lipodystrophic phenotype in adults, which may add to the background risk factor profile.\textsuperscript{5} However, the relative impact of disease, treatment, and underlying risk factor profile remains unclear. These factors are particularly hard to disentangle in adults because the timing of HIV infection itself and ART, particularly PIs, in the pathogenesis of early vascular disease, likely to be relevant to future clinical atherosclerosis.

The long-term consequences of HIV infection are particularly important for young individuals. With newer antiretroviral regimens, HIV has now become a chronic illness in developed countries. Thus, HIV-infected children have the potential to survive even to the third or fourth decade of life. Because cardiovascular disease is emerging as an important health concern at these ages, it is critically important to determine the early impact of both the HIV infection and its treatment on the arterial wall in these children.

In our study, we measured carotid IMT to assess structural disease of the arterial wall. IMT represents the cumulative burden of adverse influences operating from the earliest stages of disease. Increased IMT, shown to reflect conventional risk factor burden in children as young as 10 years of age, is an independent predictor of adverse cardiovascular outcome.\textsuperscript{17} We also assessed endothelial function, which is known to be a key event in the initiation and progression of preclinical atherosclerosis.\textsuperscript{18} In particular, reduction in local nitric oxide bioavailability, reflected by the magnitude of FMD response, is associated with a proinflammatory, proliferative, and procoagulant phenotype that establishes a locally atherogenic environment. FMD is a dynamic measure of arterial function that can be used to assess the impact of both risk factors and interventions.\textsuperscript{19,20} Using these 2 well-validated measurements of arterial structure and function, we have described the impact of disease and treatment, minimizing the effects of exposure to confounding risk factors usually present in adults.

Only 1 other study has examined the vascular changes of long-term exposure to HIV in children. FMD was impaired,
as in our study, but IMT was not increased. The extensive vascular changes in our population may be due to older age and worse disease. IMT was related to both age (a surrogate for duration of HIV) and CDC stage. The observed differences between HIV-infected children and control subjects remained after differences in the baseline characteristics between the groups were accounted for, suggesting that these changes may be related to HIV disease. Our study also raised the possibility that vascular function may be related to ART. Both IMT and FMD were impaired in children receiving ART; this was most pronounced in the PI-treated children. However, these findings must be viewed with some caution. Although PIs would not have been included or excluded on the basis of disease severity, there have been changes in the ART regimens since triple therapy became available for children in 1997. Perhaps most important is that triple therapy at that time would likely have included a PI. In recent years, however, there has been a trend toward the use of a non-nucleoside reverse-transcriptase inhibitor as first-line therapy. We have attempted to control for variables such as age that may have influenced our analyses, but more studies are required to clarify the role of ART on vascular dysfunction.

It is also unclear whether the observed vascular changes that appear to be associated with ART are driven by changes in the metabolic profile of these children. Insulin resistance and metabolic syndrome have been independently associated with vascular disease and accelerated cardiovascular disease in HIV-infected adults. Insulin resistance and the full metabolic syndrome are prevalent in overweight youth, and it has been suggested that they are increasingly prevalent in high-risk HIV-infected young people, especially blacks. In this study, we did not find major differences in BMI z scores between cases and controls and between HIV-infected children receiving different antiretroviral regimens. Further studies are required to ascertain the vascular effects of ART in childhood and to provide insight into the mechanisms contributing to vascular disease. HIV may promote atherosclerosis by activating the vascular endothelium directly or indirectly by systemic cytokine stimulation by the virus. In addition, opportunistic agents such as cytomegalovirus or herpesvirus, often present in HIV may contribute to endothelial damage.

In this study, HIV-infected children had elevated total cholesterol and cholesterol subfractions. In particular, it is interesting to note that Lp(a) levels, which are highly genetically determined, also were elevated in HIV-infected children compared with control subjects. This finding, however, must be interpreted with caution. The average Lp(a) level is higher in black than in white children, so ethnic differences may contribute to the Lp(a) variability. Furthermore, within the HIV cohort, the most pronounced changes in Lp(a) were noted in children receiving PI therapy. It is possible that increased synthesis or clearance of the particle related to HIV infection and PI therapy can account for our observed differences. The disturbances of lipids [increased total cholesterol and Lp(a) and a smaller LDL particle size] in our children receiving PIs are similar to those reported in adults but did not account for the observed vascular abnormalities. Nevertheless, the impact of lipid abnormalities on vascular disease progression in HIV certainly warrants further prospective exploration. Other mechanisms may also contribute to the adverse effect of HIV and ART on vascular disease, including enhanced expression of macrophage scavenger receptors and mitochondrial toxicity.

HIV infection and ART are associated with an atherogenic structural and functional arterial phenotype from early childhood. Because death rates among HIV-infected children have decreased 5-fold since the introduction of the highly active antiretroviral treatment, careful long-term monitoring appears warranted to detect emerging cardiovascular disease. Longitudinal studies are needed to understand the cause of vascular disease and to ascertain the contribution of different ART regimens. Pharmacological or physiological interventions may be required to prevent future vascular events in HIV-infected children.

Acknowledgments
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References


