The effect of anti–human immunodeficiency virus (HIV) treatment on hepatitis C virus (HCV) RNA levels in HIV-HCV–coinfected persons is uncertain. Although it is commonly believed that, with the initiation of HIV treatment, there may be an initial increase followed by a gradual decrease of HCV RNA levels to lower than those at pretreatment, the published studies evaluating this are of small and heterogeneous populations, are limited in follow-up, and have conflicting results. A prospective clinical trial of sufficient size and duration may help clarify this issue. This may be clinically relevant, because lower HCV RNA levels are a predictive factor for favorable response to HCV antiviral therapy.

Despite the frequency of HIV and hepatitis C virus (HCV) coinfection, the relationship among HIV infection, immunodeficiency, and HCV RNA levels is not well understood. This is particularly true when evaluating the effect of HAART on this interaction. Greater understanding is warranted, given that liver fibrosis is accelerated [1–4], time before the appearance of clinically evident liver disease is shortened [5–7], and mortality among HIV-infected patients is increased as a result of HCV-induced liver disease in HIV-HCV–coinfected patients [7]. In an effort to learn more about this issue, a MEDLINE search of English-language journals that used the key words “HCV,” “HIV,” “viremia,” and “antiretroviral” was performed to identify articles relevant to this subject. References in identified articles then were assessed for additional pertinent publications and conference abstracts. In addition, abstracts from recent HIV and infectious diseases meetings [8–16] were evaluated.

Here, we describe the apparent effect of antiretroviral therapy on HCV RNA levels from an analysis of available information; evaluate the strengths and weaknesses of these articles; and suggest a possible explanation for the findings reported in these studies. The relevance to HCV and HIV therapy in HIV-HCV–coinfected individuals is considered.

**MEASUREMENT OF HCV RNA LEVEL:**
**SYSTEMATIC AND BIOLOGIC VARIATION**

Many factors may influence the results obtained by single and serial measurement of HCV RNA levels in HIV-HCV–coinfected patients. These should be considered before discussing the effects of HAART on HCV RNA levels. The systematic variation in within-run and between-run precision of the quantitative assay used to determine HCV RNA levels (Cobas Amplicor HCV Monitor Test, version 2 [Roche Diagnostics Systems]; branched DNA 2.0 system [Chiron]; and nucleic acid sequence–based amplification assay [NASBA; Orga-
has not been evaluated specifically in HIV-HCV–coinfected cohorts; however, ample data evaluate this variation among HCV-infected subjects [17–23]. The within-run and between-run precision of the assays used in the literature are comparable [19, 20, 23]. There appears to be reasonably good concordance among branched DNA, RT-PCR, and other systems of quantifying HCV RNA levels [23]. Although preparation, handling, and storage of blood specimens submitted for testing HCV RNA levels are issues to consider, most studies suggest that HCV RNA levels remain stable [24, 25] or decrease only marginally [26] while in long-term frozen storage.

Biological factors potentially associated with HCV RNA levels include natural fluctuation over time [19, 27–31], severity of hepatocellular dysfunction [5, 29], HIV plasma viremia levels [30, 32], CD4+ T lymphocyte count [29, 31], HCV genotype [22, 33–38], and the patient’s alcohol consumption [39–41]. HCV RNA levels have been described to fluctuate by <1.5 log10 in the majority of HCV-infected, HIV-seronegative subjects in studies of 2 [19], 3 [27], and 6.6 years [28]. The information available suggests similar fluctuations in HCV RNA levels in HIV-HCV–coinfected individuals [29–31]. An increase in HCV RNA levels in HIV-HCV–coinfected patients with end-stage liver disease has been described elsewhere [29]. This may be partially explained by lower CD4+ T lymphocyte counts in these individuals.

Profound immune compromise has been associated with increased HCV RNA levels in some [29, 31], but not all [42], studies evaluating this issue. Although the major cell receptors and target cells of these 2 viruses differ, it is uncertain whether HCV replication is virologically independent of the level of HIV plasma viremia, because a correlation between HCV RNA level and HIV plasma viremia has been reported in some [31], but not all [30, 32], reports evaluating this issue. Both viruses may use CD81 cellular receptors; however, the relevance to the HIV and HCV RNA levels—and a possible correlation—is uncertain [43]. As in HIV-seronegative individuals, HCV genotype does not appear to influence HCV RNA levels in HIV-HCV–coinfected individuals [22, 33–38]. Excessive consumption of alcohol also may increase HCV RNA levels; however, the mechanism responsible for this is poorly defined [39–41].

Together, these investigations demonstrate that many factors, including systematic variation of quantitative assays and natural or biological variability of HCV RNA levels, must be considered when evaluating HCV RNA levels over time. Given the limited and problematic data currently available, it is difficult to determine with great confidence what degree of change in HCV RNA levels would be clinically significant. The following describes the perturbations in HCV RNA levels after the initiation of HAART in HIV-HCV–coinfected subjects. Further study is required to determine the biological and clinical significance of these changes.

**EARLY EFFECT OF HAART ON HCV RNA LEVELS**

The early response of HCV RNA levels to HAART remains controversial (table 1). Having considered the potential influences on HCV RNA levels measured in HIV-HCV–coinfected subjects, the effect of HAART on HCV RNA levels can be better evaluated and interpreted. Several studies suggest that HCV RNA levels may initially increase marginally in antiretroviral-treated subjects [44–47]. Puoti et al. [45] described a >0.2 log10 increase in 10 of 12 HAART-treated patients at 14 and 21 days. No difference was found between therapy consisting of protease inhibitor (PI)–based (indinavir; n = 6) or nonnucleoside reverse-transcriptase inhibitor–based (nevirapine; n = 6) treatment. However, this sample size is insufficiently powered to identify a difference, even if present.

Vento et al. [47] identified a mean HCV RNA level increase of 0.48 log10 at 1 month in 51 individuals initiating indinavir or ritonavir-based treatment. However, by month 3, the change from baseline was <0.3 log10. In this study, the HIV plasma viremia declined by a mean of 1.68 log10 over the first month; however, maximal virus load suppression, defined as HIV RNA <50 copies/mL, was not achieved in the majority of these subjects by 3 months. It is uncertain whether a larger increase in HCV RNA levels would have occurred if HIV RNA had been maximally suppressed. Rutschmann et al. [44] reported an overall mean 0.37 ± 0.13 log10 increase in HCV RNA levels, from a baseline of 5.27 ± 0.22 log10 and a >0.5 log10 increase in 9 of 19 HAART-treated subjects at 6 weeks. Once again, HIV RNA was not maximally suppressed.

An increase in HCV RNA levels shortly after the introduction of HAART has not been universally reported [46, 48, 50, 51]. These discrepancies between short-term studies may be explained by a number of factors, including different sampling times, variable HIV RNA suppression, variable duration and stages of HIV infection and immunologic status, differences between HCV assay sensitivities and accuracy, patient adherence to treatment, and antiretroviral hepatotoxicity. Although a meta-analysis might provide further insight, the above issues, indicative of the heterogeneity of these study groups and the lack of their characterization, make such an exercise inappropriate.

A pronounced clinical manifestation of this initial increase in HCV RNA levels, associated with transaminitis, signs of tender hepatomegaly, and occasionally death, is observed with the so-called immune restoration syndrome that has been described after the introduction of HAART in HIV-HCV–coinfected individuals [52–54]. The pathophysiologic explanation of the early increase in HCV RNA levels reported with this syndrome and immediately after the initiation of HAART may be cytotoxic T lymphocyte–mediated lysis of HCV-infected cells, with resulting serum alanine aminotransferase elevation and release of HCV to the plasma [44, 52, 55]. Other possible
There is evidence that IFN in combination with nucleoside reverse-transcriptase inhibitors is virologically active against HIV [57, 58]. In contrast, there is no evidence to suggest that either nucleoside reverse-transcriptase inhibitors or PIs possess direct anti-HCV activity [44, 45, 47, 48, 50, 51, 59]. There are few data assessing nonnucleoside reverse-transcriptase inhibitor anti-HCV activity, and none that are conclusive [46]. Although the study of Puoti et al. [45] was underpowered, it suggested no difference in the direction or degree of HCV RNA levels between PI and nonnucleoside reverse-transcriptase inhibitor–based therapy. Although further investigation would be ideal, the type of antiretroviral drugs used is unlikely to have a significant direct effect.

**EFFECT OF PROLONGED HAART ON HCV RNA LEVELS**

CD4+ T cell counts and functional immune competence generally increase as HIV RNA levels decrease after the introduction of HAART [60–62]. Despite several studies addressing this issue, it is unclear whether the decline in HIV RNA and increase in CD4+ T lymphocyte count, a measure of immune restoration, is associated with a reduction, an increase, or no change in HCV RNA levels (table 2). At least 1 study described a reduction in HCV RNA levels by >0.5 log_{10} after 12 months of treatment in 7 of 16 patients receiving HAART, with HIV RNA levels suppressed to <50 copies/μL [50]. This, in fact, is the only long-term evaluation of HCV RNA levels in which HIV

### Table 1. Effect of HAART on hepatitis C virus (HCV) RNA levels during the initial 3 months of therapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Antiretroviral therapy</th>
<th>Baseline CD4 count, cells/μL</th>
<th>Baseline, log_{10}</th>
<th>Month 1–2, log_{10}</th>
<th>Change at month 1–2</th>
<th>Month 3, log_{10}</th>
<th>Change at month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutschmann et al. [44]</td>
<td>19</td>
<td>PI + 2 NRTIs</td>
<td>63 ± 13</td>
<td>5.27 ± 0.22</td>
<td>Δ0.37 ± 0.13</td>
<td>Increase (P = .01)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Puoti et al. [45]</td>
<td>12</td>
<td>Idv (6) or Nvp (6), 3TC, d4T</td>
<td>338 ± 93</td>
<td>7.0 ± 0.2</td>
<td>Δ0.03 ± 0.1</td>
<td>Increase (P = NS)</td>
<td>Δ−0.18 ± 0.16</td>
<td>Decrease (P = NS)</td>
</tr>
<tr>
<td>Matsiotas-Bernard et al. [46]</td>
<td>10</td>
<td>PI plus 2 NRTIs</td>
<td>84 ± 57</td>
<td>4.59 ± 0.53</td>
<td>ΔNil</td>
<td>NC</td>
<td>ΔNil</td>
<td>NC</td>
</tr>
<tr>
<td>Vento et al. [47]</td>
<td>21</td>
<td>Idv, 3TC, + Zdv</td>
<td>316</td>
<td>5.54</td>
<td>6.05</td>
<td>Increase</td>
<td>5.81</td>
<td>Increase</td>
</tr>
<tr>
<td>Zylberberg et al. [48]</td>
<td>11</td>
<td>Idv, 3TC, + d4T</td>
<td>332</td>
<td>5.58</td>
<td>6.02</td>
<td>Increase</td>
<td>5.87</td>
<td>Increase</td>
</tr>
<tr>
<td>Zylberberg et al. [48]</td>
<td>19</td>
<td>Rtv, Zdv, + 3TC</td>
<td>325</td>
<td>5.52</td>
<td>5.99</td>
<td>Increase</td>
<td>5.81</td>
<td>Increase</td>
</tr>
<tr>
<td>Rockstroh et al. [49]</td>
<td>22</td>
<td>PI + 2 NRTIs</td>
<td>119 ± 118</td>
<td>5.5 ± 0.8</td>
<td>NR</td>
<td>NR</td>
<td>5.3 ± 0.7</td>
<td>Decrease (P = NS)</td>
</tr>
<tr>
<td>Rockstroh et al. [49]</td>
<td>13</td>
<td>Sqv, 3TC, Zdv, or d4T</td>
<td>179 ± 139</td>
<td>6.56 ± 6.04</td>
<td>NR</td>
<td>NR</td>
<td>6.46 ± 5.86</td>
<td>Decrease (P = NS)</td>
</tr>
<tr>
<td>Perez-Olmeda et al. [50]</td>
<td>13</td>
<td>Idv, 3TC, Zdv, or d4T</td>
<td>38 ± 41</td>
<td>6.54 ± 5.95</td>
<td>NR</td>
<td>NR</td>
<td>6.52 ± 5.95</td>
<td>Decrease (P = NS)</td>
</tr>
<tr>
<td>Perez-Olmeda et al. [50]</td>
<td>16</td>
<td>PI + 2 NRTIs</td>
<td>NR</td>
<td>~7</td>
<td>NR</td>
<td>NR</td>
<td>~7</td>
<td>NC (P = NS)</td>
</tr>
</tbody>
</table>

**NOTE.** d4T, stavudine; Idv, indinavir; NC, no change in HCV RNA; NR, not reported; NRTI, nucleoside reverse-transcriptase inhibitor; Nvp, nevirapine; PI, protease inhibitor; Rtv, ritonavir; Sqv, saquinavir; Zdv, zidovudine; 3TC, lamivudine.

* P values that are stated were reported.

a Mean change in virus load reported, as opposed to change in group mean.
Table 2. Long-term effect of HAART on hepatitis C virus (HCV) RNA levels.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Antiretroviral therapy</th>
<th>Baseline CD4 count, cells/μL</th>
<th>HCV RNA level Baseline, ( \log_{10} )</th>
<th>Month 4–6, ( \log_{10} )</th>
<th>Month 9–12, ( \log_{10} )</th>
<th>Change</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutschmann et al. (^{a}) [44]</td>
<td>19</td>
<td>PI ± NRTI(s)(^{b})</td>
<td>63 ± 13</td>
<td>5.27 ± 0.22</td>
<td>Δ−0.16 ± 0.23</td>
<td>Δ−0.14 ± 0.19</td>
<td>Decrease</td>
<td>NS</td>
</tr>
<tr>
<td>Matsiota-Bernard et al. (^{a}) [46]</td>
<td>10</td>
<td>PI + 2 NRTIs</td>
<td>84 ± 57</td>
<td>4.59 ± 0.53</td>
<td>ΔNC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zylberberg et al. [53]</td>
<td>22</td>
<td>PI + 2 NRTIs</td>
<td>119 ± 118</td>
<td>5.5 ± 0.8</td>
<td>5.3 ± 0.3</td>
<td>5.3 ± 0.3</td>
<td>Decrease</td>
<td>NS</td>
</tr>
<tr>
<td>Perez-Olmeda et al. [50]</td>
<td>16</td>
<td>PI + 2 NRTIs</td>
<td>NR</td>
<td>−7</td>
<td>NR</td>
<td>−6</td>
<td>Decrease</td>
<td>NR</td>
</tr>
<tr>
<td>Yokozaki et al. [32]</td>
<td>25</td>
<td>PI + 2 NRTIs</td>
<td>∼325</td>
<td>−6.95</td>
<td>−6.78</td>
<td>−6.6</td>
<td>Decrease</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ragni et al. [38]</td>
<td>21</td>
<td>PI + 2 NRTIs</td>
<td>152</td>
<td>7.15</td>
<td>7.05</td>
<td>7.30</td>
<td>Increase</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Bush et al. [63]</td>
<td>21</td>
<td>HAART</td>
<td>NR</td>
<td>5.78</td>
<td>5.81</td>
<td>NR</td>
<td>Increase</td>
<td>NR</td>
</tr>
<tr>
<td>Gavazzi et al. [64]</td>
<td>10</td>
<td>PI + 2 NRTIs</td>
<td>172 ± 121</td>
<td>5.28 ± 0.26</td>
<td>NR</td>
<td>5.39 ± 0.26</td>
<td>Increase</td>
<td>NS</td>
</tr>
<tr>
<td>Vento et al. [47]</td>
<td>12</td>
<td>PI + 2 NRTIs</td>
<td>202 ± 98</td>
<td>4.65 ± 0.32</td>
<td>NR</td>
<td>4.82 ± 0.33</td>
<td>Increase</td>
<td>NS</td>
</tr>
<tr>
<td>Vento et al. [47]</td>
<td>21</td>
<td>Idv, 3TC, + Zdv</td>
<td>316</td>
<td>5.54</td>
<td>NR</td>
<td>5.66</td>
<td>Increase</td>
<td>NR</td>
</tr>
<tr>
<td>Torre et al. [65]</td>
<td>65</td>
<td>HAART</td>
<td>NR</td>
<td>6.53</td>
<td>NR</td>
<td>6.63(^{c})</td>
<td>Increase</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** d4T, stavudine; Idv, indinavir; NC, no change in HCV RNA; NR, not reported; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; Rtv, ritonavir; Zdv, zidovudine; 3TC, lamivudine.

\(^{a}\) Mean change in virus load reported, as opposed to change in group mean.

\(^{b}\) The plus/minus sign (±) indicates with or without an NRTI.

\(^{c}\) Data at 24 months.

RNA levels were maximally suppressed with antiretroviral therapy. The mean CD4\(^+\) T lymphocyte increase at 12 months was 210 ± 18 cells/μL, which is indicative of significant immune restoration. In this cohort, HCV RNA levels fell below the limit of detection (100–1000 HCV RNA copies/mL) in 4 of 16 subjects. This has been reported elsewhere in 2 of 31 \[32\] and 2 of 10 \[59\] subjects after the initiation of HAART; however, most other studies suggest that clearance of HCV is not usual in HIV-HCV–coinfected subjects. Nonetheless, these results suggest that prolonged suppression of HIV replication associated with immunologic restoration may result in improved immune control of HCV infection.

Yokozaki et al. \[32\] assessed 25 HIV-HCV–coinfected subjects at baseline and at 6 and 12 months after the introduction of HAART. At baseline, the mean HCV RNA level was ∼9 × 10\(^6\) genome equivalents per milliliter (Eq/mL), using a branched DNA probe (Quantiplex HCV RNA; Chiron). The mean HCV RNA levels had decreased to ∼6 × 10\(^6\) Eq/mL by 6 months and to ∼4 × 10\(^6\) Eq/mL by 12 months. When transformed to log\(_{10}\) values, this reflects a change of 0.2–0.4 log\(_{10}\) Eq/mL. The biological relevance of this is unclear. This study is limited by its failure to report exact values and by the reporting of results as a group mean, as opposed to the degree and direction of change for each individual. Furthermore, the HIV assay lower limit of detection was 400 HIV RNA copies/mL, a measure that, by current standards of measurement and treatment, is not maximally suppressed.

Other studies assessing the long-term effect of HAART on HCV RNA levels with data at 3 \[45, 49\], 4 \[44\], 6 \[39, 46\], 9 \[48\], 12 \[64\], and 24 \[65\] months after the initiation of HAART have not duplicated the above findings. In a study that lasted 24 months, Torre et al. \[65\] reported a small, statistically insignificant change in HCV RNA levels in 65 HIV-HCV–coinfected subjects receiving HAART. Furthermore, change in HCV plasma viremia was evaluated as a function of baseline alanine aminotransferase level and on whether immune restoration, defined as an increase in CD4 T cell count from <200 cells/μL at baseline to ≥400 cells/μL at 12 and 24 months, was...
achieved. These parameters did not appear to influence the effect of long-term HAART on HCV RNA levels. As in other studies, HIV RNA was not maximally suppressed, and a subgroup analysis of those achieving maximal HIV virologic suppression was not performed.

These studies are limited by the fact that they report only the changes in group mean over time and do not comment on the amount and direction of change for individuals. Furthermore, in several of these studies, follow-up for all individuals contributing to the baseline group mean HCV RNA measurement is not complete [44, 48, 65] or is not clearly stated [64], thereby making comparison between HCV RNA levels at baseline and time points thereafter problematic. It should not be assumed that the baseline level of HCV RNA levels or that the degree and direction of change in this measure after the initiation of HAART was the same for those with complete follow-up measurements and for those without. An additional concern is that most of these studies only assess 2 time points, one at baseline and one other subsequent measure. Ideally, multiple time points are required to detect and measure a relationship between progressive immune restoration from HAART and HCV RNA levels.

Further confusing this issue are 2 studies describing an increase in HCV RNA levels at 48 and 96 weeks of HAART [39, 66]. In these studies, the change in HCV RNA levels described was $<0.3 \log_{10}$ a magnitude of change explicable by biological and systematic variability and by chance. In addition, this minimal change in HCV RNA levels is of uncertain biological relevance. A significant problem with each of these studies is that HIV RNA was not maximally suppressed (i.e., $<50$ HIV RNA copies/mL); therefore, for this reason, it can be argued that optimal immune restoration was not achieved. These studies are small and underpowered. Once again, mean group HCV RNA levels were reported, but a clear description of within-subject variability of this measure over time is missing, and follow-up is not complete.

**EFFECT OF DISCONTINUATION OF HAART ON HCV RNA LEVELS**

An interesting but minimally explored question is the effect of HAART discontinuation or virologic HIV treatment failure on HCV RNA levels. Bush et al. [63] described a cohort of 21 HIV-HCV–coinfected subjects with a median HIV RNA level of $<400$ copies/mL 4 months after the initiation of HAART. The illness of 8 of these subjects subsequently failed to respond to antiretroviral therapy. A median increase in HCV RNA levels to $6.3 \log_{10}$ copies/mL was reported in these 8 individuals, from $5.78 \log_{10}$ copies/mL at baseline and $5.81 \log_{10}$ copies/mL at 4 months. This issue merits further exploration.

**CLINICAL RELEVANCE OF HCV RNA LEVELS IN HIV-HCV COINFECTION**

If present, a reduction in HCV RNA levels as a result of initial HIV therapy could justify deferral of HCV treatment in HIV-HCV–coinfected individuals for 2 reasons. There appears to be a continuous relationship between HCV RNA level and the likelihood of sustained response to IFN and ribavirin antiviral therapy, defined as plasma HCV RNA level negativity 6 months after completion of treatment [67–70]. In subjects with HCV RNA levels $>2.0 \times 10^5$ HCV RNA copies/mL, as measured by the National Genetics Institute HCV SuperQuant system (equivalent to $\sim 2.0 \times 10^7$ HCV RNA copies/mL by the Roche Amplicor HCV Monitor system), the sustained response after 48 weeks of IFN and ribavirin was 36%, compared with 43% for those with HCV RNA levels below this level [68]. The importance of HCV RNA level also has been demonstrated in other studies [70]. It is reasonable to assume that the same is true in HIV-HCV–coinfected subjects. If HCV RNA level is indirectly reduced by potent and durable antiretroviral treatment, then the likelihood of responding to IFN and ribavirin therapy with sustained clearance of HCV RNA levels may be increased. If this assumption is demonstrated to be true, then, given the incomplete efficacy of current HCV treatment, a strong rationale would be provided for the delay of HCV antiviral therapy until after effective HIV antiretroviral therapy was established.

Among immunocompetent hosts, HCV RNA levels vary greatly in individuals with HCV infection and, in most reports, do not correlate with or predict the progression of liver disease [68, 70]. It is uncertain whether the same is true in immunocompromised, HIV-HCV–coinfected individuals. Because HCV RNA levels are higher and liver fibrosis occurs more rapidly in HIV-HCV–coinfected subjects, it is plausible that there is a correlation between HCV RNA levels and progression of liver disease in this population. A retrospective study assessing liver fibrosis scores before and a median of 14 months after PI-based antiretroviral therapy in HIV-HCV–coinfected subjects suggests that the rate of fibrosis progression was significantly slower in patients treated with a PI and nucleoside reverse-transcriptase inhibitors, compared with those treated only with nucleoside reverse-transcriptase inhibitors [71]. It is unclear whether these findings were a result of an indirect HAART-induced decline in HCV RNA levels, improved HCV-specific immune response, a direct PI effect on fibrosis matrix synthesis, or a combination of these factors.

**CONCLUSION**

Although several studies attempt to describe the natural history of HCV RNA levels after the initiation of HAART, no single
report clearly describes it from the introduction of therapy to a point when antiretroviral activity is well established and immune reconstitution is equilibrated. Many of these investigations are of small size, thereby limiting the ability to draw meaningful conclusions. Almost all results are based on subjects without maximal therapeutic suppression of HIV RNA. The effect that discontinuing HAART or failing to respond to HAART may have on HCV RNA levels is uncertain. A critical review of the literature demonstrates that the natural history of HCV RNA levels in HAART-treated, HIV-HCV–coinfected individuals remains to be fully defined. A well-designed, prospective study of sufficient power and duration is needed to clarify these issues.

References


