Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): a balancing act

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Advances in highly active antiretroviral therapy (HAART) options for people living with HIV/AIDS have resulted in decreased morbidity and mortality. To some extent, the role of disease progression in eroding quality of life (QOL) erosion in the pre-HAART age is now supplanted by drug toxicities, one of the Achilles’ heels of HAART. This article reviews research findings on treatment and QOL outcomes a decade into the HAART era.

Keywords: AIDS, drug toxicities, QOL

Introduction

A quarter of a century after the initial reports of HIV infection in the industrialized world, the global HIV/AIDS pandemic continues to spread relentlessly, with nearly 40 million people infected worldwide as of 2006.1 Since the advent of highly active antiretroviral therapy (HAART) in 1996, HIV-related mortality and morbidity rates have plummeted in areas with access to antiretrovirals (ARVs).2,3 Newer medications are continually being developed for clinical use, expanding the current armamentarium of ARVs to include over 20 agents in five distinct pharmacological classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors and, most recently, integrate inhibitors. Yet the challenges associated with successful HAART are significant, as clinicians and patients strive to balance adherence, efficacy, tolerability and toxicity. Herein, we outline the major drug toxicities of antiretroviral therapy and discuss their impact on quality of life (QOL).

Classification of side effects of antiretroviral agents

For the purposes of this discussion, it is useful to group the important toxicities of HAART according to symptom presentation and symptom duration (Table 1). Primary among the symptomatic chronic toxicities is diarrhoea, particularly with PI-based regimens. This side effect is often accompanied by other gastrointestinal complaints such as nausea, vomiting and bloating. In published clinical trials of modern HAART regimens, rates of grade 2–4 diarrhoea were 11% to 16%, 2% to 3% and 6% to 13% with ritonavir-boosted lopinavir-, atazanavir- and fosamprenavir-based regimens, respectively.4–7 Much of this toxicity is thought to be related to the ritonavir component, but the important pharmacological boosting effect of this drug on the companion PI means that ritonavir boosting remains a preferred therapeutic strategy in published guidelines.8,9 Rates of grade 2–4 diarrhoea from trials of newer PIs in treatment-experienced patients are similar, at 10.9% for tipranavir/ritonavir (versus 9.4% for comparator PIs) and 3% for darunavir/ritonavir (versus 3% with comparator PIs).10,11

Anaemia is a well-recognized toxicity of zidovudine that can be treatment-limiting. The cardinal symptoms of fatigue and shortness of breath on exertion usually compromise physical capacity and role functioning (i.e. time spent or performance in work or other usual activities). In the recently reported Study 934, the incidence of anaemia as a side effect for zidovudine/ lamivudine in combination with efavirenz (5%) was significantly higher than for tenofovir/efavirenz combination with efavirenz (<1%).12 Anaemia was the major factor driving the higher rate of drug discontinuations in the zidovudine/lamivudine arm (9% versus 4%) and the higher proportion of patients in the tenofovir/efavirenz arm reaching and maintaining the primary endpoint of <400 copies/mL HIV RNA at 48 weeks. Large cohort studies have consistently demonstrated that anaemia in HIV-infected individuals is an important predictor of mortality.13,14

Lipodystrophy is another important chronic toxicity, but its heterogeneity has plagued attempts to characterize its frequency and underlying aetiology. An international case–control study thus included a combination of multiple demographic, clinical,
Chronic, symptomatic

Table 1. Antiretroviral toxicities

<table>
<thead>
<tr>
<th>Category</th>
<th>Toxicity</th>
<th>Common culprits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic, symptomatic</td>
<td>diarrhoea</td>
<td>PIs, NRTIs</td>
</tr>
<tr>
<td></td>
<td>lipodystrophy</td>
<td>zalcitabine, a, didanosine, stavudine</td>
</tr>
<tr>
<td></td>
<td>anaemia</td>
<td>enfuvirtide</td>
</tr>
<tr>
<td></td>
<td>peripheral neuropathy</td>
<td>efavirenz, zalcitabine, a</td>
</tr>
<tr>
<td></td>
<td>neuropysychiatric</td>
<td></td>
</tr>
<tr>
<td></td>
<td>injection site reactions</td>
<td></td>
</tr>
<tr>
<td>Acute, symptomatic</td>
<td>rash</td>
<td>NNRTIs, any drug abacavir, any drug</td>
</tr>
<tr>
<td></td>
<td>hypersensitivity</td>
<td>efavirenz, didanosine</td>
</tr>
<tr>
<td></td>
<td>neuropysychiatric</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Chronic or acute, may be</td>
<td>dyslipidaemia</td>
<td>PIs, NRTIs</td>
</tr>
<tr>
<td>symptomatic or asymptomatic</td>
<td>insulin resistance</td>
<td>PIs, NRTIs</td>
</tr>
<tr>
<td></td>
<td>renal tubular toxicity</td>
<td>tenofovir, unknown</td>
</tr>
<tr>
<td></td>
<td>osteopenia</td>
<td>NRTIs</td>
</tr>
<tr>
<td></td>
<td>hyperlactataemia</td>
<td>PIs, NNRTIs, (nevirapine), NRTIs</td>
</tr>
</tbody>
</table>

*aZalcitabine is no longer available.*

Health-related QOL is best assessed from the perspective of the individual patient, and much of the literature is thus based on studies in which patients score their QOL using previously validated scales. These scales present a numerical rating of QOL on a gradient ranging from low to high. QOL ratings may be altered in response to intrusive symptoms; side effects are also tantamount to symptoms. Deteriorations in QOL due to illness symptoms in the pre-HAART era may have been largely replaced by equally important deteriorations due to side effects in the HAART era. A key challenge for researchers and healthcare providers has been determining the clinical factors, such as specific identifiable symptoms or ARV toxicities, affecting QOL as well as the magnitude of these influences.

The conundrum: comparing QOL pre- and post-HAART

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HIV-related symptoms attributable to both the underlying disease and treatment-associated adverse events affect a wide range of components of well-being. Although a formal meta-analysis of the existing literature has not been carried out to our knowledge, the overall impact of each discrete symptom or side effect, as judged by β values in regression analyses or estimated by effect size calculations, appears to be in the range of one-quarter to one-half effect size equivalent. In simpler terms, the presence of three symptoms or side effects, for example, is generally thought to yield deterioration in QOL equivalent to approximately one standard deviation. Much of the QOL research in the HIV field suggests that one standard deviation is generally equivalent to ~10% to 20% in scaled terms (e.g. 10–20 points on a 0–100 scale). By extension, the elimination of symptoms or side effects might be expected to result in QOL improvement of a similar magnitude (i.e. reducing three symptoms or side effects raises a QOL rating by an approximate equivalent of one standard deviation). If study findings suggest a relation between QOL and immunological factors, such as CD4 count, or virological factors, such as viral load, it is still likely that the lived experience of symptoms and/or side effects, variables clinically related to immunological and virological parameters, are actually most responsible for the variance in QOL ratings. Factors such as perceived social support and other psychological issues may predict QOL and play a mediating role in the subjective experience of distress related to symptomatology. However, the focus of our discussion is the interaction of clinical side effects and well-being.

Most pre-HAART research investigating QOL changes among people living with HIV/AIDS (PHA) was conducted over relatively short time periods, usually no longer than a 1 year duration. These studies generally revealed consistent patterns of QOL deterioration over time for PHA, especially for those who progressed to AIDS-defining illnesses. Since the introduction of HAART more than a decade ago, interest in the effects of more promising treatment regimens on both life prolongation and quality of life supplanted the earlier trend of characterizing the relation between disease progression and well-being. However, the breadth of published literature on QOL changes over time is surprisingly small. In contrast to pre-HAART trends, the general pattern of results of HAART-era studies is one of little change or modest improvement in average QOL ratings for PHA over periods of <2 years. There is a paucity of post-HAART research extending over longer (i.e. 2–4 year) time periods, with results similar to those of shorter duration in the HAART era. For the most part, mean QOL ratings appear to remain stable in spite of viral suppression and immunological repletion. This suggests that within-sample variability in QOL ratings appears to result from the alleviation of disease symptoms in tandem with emerging side effects for those with symptomatic disease during HAART initiation and from the development of toxicities for those who are initially asymptomatic. An interesting question is whether or not the potential improvements in QOL during a structured, negotiated or patient-initiated treatment interruption may counterbalance or outweigh the health benefits of HAART. However, the reported quality research on this topic is lacking, with most findings based on biased samples and retrospective rather than prospective designs, and further discussion of this topic is not within the scope of our paper.

Some of the specific features that have drawn the most attention in HIV-related QOL research are diarrhoea, anaemia and lipodystrophy syndrome. Diarrhoea can have a significant negative impact on QOL and be responsible for decreased functional ability, social functioning, mental health and general health perceptions.

Research with patients on HAART found that those with diarrhoea had poorer QOL ratings compared with matched controls without diarrhoea. These findings are corroborated in qualitative research in which diarrhoea produced a debilitating impact on daily and social life, energy, emotional well-being and sexual function. Diarrhoea may be managed, and some degree of improvement in QOL can be achieved, through conservative measures such as diet modification and loperamide use.

The effects of anaemia on overall functioning and well-being for PHA have been well described. The alleviation of anaemia through the treatment of co-existing disease conditions, discontinuation of culprit drugs and/or recombinant human erythropoietin is associated with improved QOL.

Research employing open-ended survey techniques, single-item questions thematically associated with body changes or other grounded qualitative study methods corroborated initial apprehensions concerning the effects of lipodystrophy syndrome on QOL. However, one of the first published studies in which a standardized QOL measure was employed did not find significant differences in ratings of patients with clinically defined lipodystrophy compared with those without lipodystrophy. In another study, patients with lipodystrophy-related body changes were twice as likely to feel recognizable as being HIV-positive yet were not different in attitudes to health condition or self-reported general well-being compared with patients with no evidence of lipodystrophy. Similarly, a study systematically examining the relationship between severity of lipodystrophy and a broad range of standardized measures of QOL and mental health among PHA with physically visible manifestations of lipodystrophy found minimal associations, with the exception of a marked impact of lipodystrophy on self-perceived body image. Body image ratings were below the 10th percentile for the majority of the study sample, using body image normative values for the general population as the reference standard, and body image ratings were inversely associated with the severity of lipodystrophy reported. Given that the overall reported symptom and side effect profile were significantly associated with mental health and QOL ratings in that study, it may be that standardized instruments are poorly equipped for detecting the effects of lipodystrophy-related body changes on QOL in general, but are well equipped for capturing the effects on body self-concept. One additional study found that patients with lipodystrophy reported higher rates of body-related concerns and associated effects on psychological and social domains of QOL compared with a control group of PHA without lipodystrophy, though the former group was not more likely to report a desire to avoid sexual intimacy.

Life in the HAART age: the balancing act
As can be seen, length of life and QOL in the HAART age is a delicate system difficult to keep in balance. ARV therapy has the potential to confer significant benefits by controlling HIV disease and extending life, while posing unpleasant side effects.
that erode QOL. Maintaining or improving QOL, therefore, depends on paying careful attention to the management of disease progression, illness symptoms and treatment side effects. Questions concerning the salutary effects of immunological restoration juxtaposed with the potential for adverse treatment effects remain at the forefront of outcome research for the HIV-infected population.

Transparency declarations

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References

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