Delayed Progression to Death and to AIDS in a Hong Kong Cohort of Patients with Advanced HIV Type 1 Disease During the Era of Highly Active Antiretroviral Therapy

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Background. The magnitude of the impact of highly active antiretroviral therapy (HAART) since its introduction in non-Western countries is not entirely clear. We studied disease progression among adult patients with advanced human immunodeficiency virus type 1 (HIV-1) infection in the pre-HAART (i.e., 1996 and earlier) and HAART eras in Hong Kong.

Methods. The cohort of patients seen at the Integrated Treatment Center (Hong Kong) from 1984 through mid-2003 was retrospectively examined with respect to 3 clinical end points: death after the diagnosis of acquired immunodeficiency syndrome (AIDS), progression to AIDS after achieving a CD4 cell count of <200 cells/μL, and death after achieving a CD4 cell count of <200 cells/μL.

Results. A total of 581 patients with advanced HIV-1 disease had AIDS and/or a CD4 cell count of <200 cells/μL. The incidences of death after AIDS (52.3% vs. 13.6%), AIDS progression after a CD4 cell count of <200 cells/μL (47.7% vs. 20.9%), and death after a CD4 cell count of <200 cells/μL (38.8% vs. 7.0%) were significantly higher among patients in the pre-HAART era than among those in the HAART era (P < .001 for all). On the basis of life-table analysis, the probabilities of death after AIDS (P < .0001), AIDS after a CD4 cell count of <200 cells/μL (P = .0063), and death after a CD4 cell count of <200 cells/μL (P < .0001) diminished in the HAART era, compared with the pre-HAART era. Median survival after AIDS increased from 29.8 months during the pre-HAART era to >70 months during the HAART era (P < .001). Compared with patients in the pre-HAART era, adjusted hazard ratios of clinical events were 0.15 (95% confidence interval [CI], 0.08–0.26) for death after AIDS, 0.38 (95% CI, 0.24–0.60) for AIDS after a CD4 cell count of <200 cells/μL, and 0.25 (95% CI, 0.15–0.40) for death after a CD4 cell count of <200 cells/μL for patients in the HAART era.

Conclusions. The clinical outcome of patients with advanced HIV-1 disease in Hong Kong significantly improved during the HAART era. Our findings of extended durations of survival and AIDS-free status may be relevant to the expected health impacts associated with increased access to HAART in non-Western countries.
Kong was initially treated with zidovudine monotherapy in 1987, followed by dual nucleoside analogue therapy in 1994. Locally, HAART became the standard treatment in 1997 [3]. Thus, the situation in Hong Kong could be examined to shed some light on the health impacts of HAART in non-Western countries. This is especially relevant as the World Health Organization aims to increase the global access to HAART [4]. Against this background, we set out to study HIV disease progression in patients treated at our clinic (Integrated Treatment Center, Hong Kong) in the pre-HAART and HAART eras. Specifically, we wished to gauge the extent of the health impacts and to elucidate their associated factors in patients with advanced HIV-1 disease.

METHODS

Study population. Since the report of the first Hong Kong patients with AIDS in 1984, the government has set up and operated a designated HIV clinical service in the Hong Kong Department of Health. The study population was the cohort of patients who had attended our HIV clinic by the end of June 2003. We excluded patients who were infected perinatally or were ≤13 years of age at the time of HIV diagnosis, because the progression of HIV disease in such individuals differs from that in adults [5].

Data collection. Data was collected retrospectively from a clinical information system that tracks our HIV clinic cohort. Information examined in this study included demographic characteristics, HIV/AIDS diagnosis, CD4 cell count, and clinical outcome. Patients were divided into 2 groups on the basis of the year in which they received a diagnosis of HIV infection; patients in the pre-HAART group received their diagnosis during 1984–1996, and patients in the HAART group received their diagnosis between 1997 and mid-2003. All data was censored after 30 June 2003. The surveillance case definition of AIDS that was used in Hong Kong for adults and adolescents was employed in the present study [6]. Locally, AIDS is defined as the occurrence of clinical events that appear in the Centers for Disease Control and Prevention 1993 expanded surveillance case definition [7], with the following modifications: pulmonary or cervical lymph node tuberculosis is counted only if

### Table 1. Demographic and clinical characteristics of patients with advanced HIV-1 disease (AIDS and/or a CD4 cell count of <200 cells/μL) in the pre-HAART (1984–1996) and HAART (1997 to mid-2003) eras.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>All (n = 581)</th>
<th>Pre-HAART era (n = 278)</th>
<th>HAART era (n = 303)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>.036</td>
</tr>
<tr>
<td>Male</td>
<td>500 (86.1)</td>
<td>248 (89.2)</td>
<td>252 (83.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>81 (13.9)</td>
<td>30 (10.8)</td>
<td>51 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>.013</td>
</tr>
<tr>
<td>Chinese</td>
<td>457 (78.7)</td>
<td>206 (74.1)</td>
<td>251 (82.8)</td>
<td></td>
</tr>
<tr>
<td>Non-Chinese</td>
<td>124 (21.3)</td>
<td>72 (25.9)</td>
<td>52 (17.2)</td>
<td></td>
</tr>
<tr>
<td>HIV exposure category</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td>365 (62.8)</td>
<td>142 (51.1)</td>
<td>223 (73.6)</td>
<td></td>
</tr>
<tr>
<td>Male-male sex</td>
<td>178 (30.6)</td>
<td>107 (38.5)</td>
<td>71 (23.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>38 (6.5)</td>
<td>29 (10.4)</td>
<td>9 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Age at time of HIV diagnosis, years</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>37.0 ± 10.5</td>
<td>35.1 ± 10.1</td>
<td>38.8 ± 10.6</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>35.7</td>
<td>33.5</td>
<td>37.3</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count at time of HIV diagnosis, cells/μL</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>184.3 ± 194.6</td>
<td>270.7 ± 231.1</td>
<td>133.0 ± 147.3</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>118.0 (1–1370)</td>
<td>202.0 (4–1370)</td>
<td>74.5 (1–1039)</td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/μL</td>
<td>305 (52.5)</td>
<td>84 (30.2)</td>
<td>221 (72.9)</td>
<td></td>
</tr>
<tr>
<td>Follow-up duration, patient-months</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total</td>
<td>25,789.3</td>
<td>16,702.5</td>
<td>9086.9</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44.4 ± 37.7</td>
<td>60.1 ± 44.5</td>
<td>30.0 ± 21.9</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>36.6 (0–177.2)</td>
<td>55.8 (0–177.2)</td>
<td>25.6 (0–76.4)</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>316 (54.4)</td>
<td>176 (63.3)</td>
<td>140 (46.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD4 cell count &lt;200 cells/μL</td>
<td>558 (96.0)</td>
<td>258 (92.8)</td>
<td>300 (99.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Without AIDS before or at diagnosis of initial CD4 cell count &lt;200 cells/μL</td>
<td>401 (69.0)</td>
<td>195 (70.1)</td>
<td>209 (69.0)</td>
<td>.023</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated.
patient has a CD4 cell count of <200 cells/μL, and disseminated *Penicillium marneffei* infection is included in the list of AIDS-defining conditions. A CD4 cell count of <200 cells/μL without AIDS-defining illness was not considered to be AIDS in Hong Kong and was not regarded as such in this study.

In the present study, we focused on disease progression in patients with advanced HIV-1 infection—that is, those with AIDS and/or a CD4 cell count of <200 cells/μL. The assessment of disease progression was based on 3 clinical end points: death among patients with AIDS, progression to AIDS in patients initially without AIDS and with a CD4 cell count of <200 cells/μL, and death among patients with a CD4 cell count of <200 cells/μL. The time to these end points or, on the contrary, the time to the end of the follow-up or study periods without occurrence of these end points reflect disease progression rates in the pre-HAART and HAART era. Patients who had reached the end points before the start of the observation period were excluded. For example, a patient who had already progressed to AIDS before the CD4 cell count decreased to <200 cells/μL would not have been included in the analysis of the second clinical end point.

**Statistical analysis.** Observed differences in categorical and continuous variables between the pre-HAART and HAART eras were compared using the χ² test (for categorical variables) and the Mann-Whitney U test (for continuous variables). A P value of <.05 was taken to be statistically significant for differences between groups. Using life-table analysis, we compared the cumulative probability and the median time to the 3 clinical end points in the 2 treatment eras. The relative risks of reaching both the end points and their associated factors were obtained by Cox proportional hazards models, using both univariate and multivariate analyses. Hazard ratios (HRs) and 95% CIs are presented. We used SPSS, version 11.0 (SPSS), for statistical analysis.

**RESULTS**

A total of 1074 HIV-1–infected patients were treated during the study period, of whom 581 (54.1%) had advanced disease. There were significantly more female, more Chinese, and more heterosexual patients with advanced HIV-1 disease during the HAART era (table 1). Patients in the pre-HAART era were younger, had a higher median CD4 cell count at the time of HIV diagnosis, and had been observed for a longer period of

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### Table 2. Progression to clinical end points of AIDS or death among 581 patients with advanced HIV-1 disease in the pre-HAART (1984–1996) and HAART (1997–mid 2003) eras.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Pre-HAART era</th>
<th>HAART era</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death after AIDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>92/176 (52.3)</td>
<td>19/140 (13.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>47/176 (26.7)</td>
<td>111/140 (79.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>37/176 (21.0)</td>
<td>10/140 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Follow-up duration, patient-months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4786.3</td>
<td>3787.8</td>
<td>.099</td>
</tr>
<tr>
<td>Mean ± SD (median)</td>
<td>27.2 ± 30.0</td>
<td>27.1 ± 22.1</td>
<td>18.9</td>
</tr>
</tbody>
</table>

| **AIDS after a CD4 cell count <200 cells/μL** |                   |             |     |
| Yes            | 93/195 (47.7) | 43/206 (20.9) | <.001 |
| No             | 85/195 (43.6) | 145/206 (70.4) |       |
| Unknown       | 17/195 (8.7)  | 18/206 (8.7)  |       |
| Follow-up duration, patient-months |                   |             |     |
| Total         | 6697.5        | 4341.1      | .002 |
| Mean ± SD     | 33.8 ± 33.3   | 21.1 ± 22.6 |       |
| Median        | 24.6          | 13.1        |       |

| **Death after a CD4 cell count of <200 cells/μL** |                   |             |     |
| Yes           | 100/258 (38.8) | 21/300 (7.0)  | <.001 |
| No            | 113/258 (43.8) | 252/300 (84.0) |       |
| Unknown      | 45/258 (17.4)  | 27/300 (9.0)  |       |
| Follow-up duration, patient-months |                   |             |     |
| Total         | 10,663.4      | 7879.5      | <.001 |
| Mean ± SD    | 41.3 ± 32.3   | 26.3 ± 22.3 |       |
| Median       | 34.3          | 18.3        |       |

**NOTE.** Data are no. of patients with the characteristic/total no. evaluated (%), unless otherwise indicated.

* Lost to follow-up before the end of the study period.
time. The total number of patients with advanced disease at the start of the evaluation period for each of the 3 clinical outcomes ranged from 316 to 558, with an overlap of subjects across groups (tables 1 and 2).

As shown in table 2, there were significantly fewer patients with advanced disease in the HAART era who achieved ≥1 of the 3 clinical end points, compared with patients with advanced disease in the HAART era (P < .001 for all end points). Although the median follow-up duration of 17–19 months after the progression to AIDS was similar, only 13.6% of HAART-era patients died, compared with >50% of pre-HAART-era patients. However, the median durations of follow-up for the 2 end points of progression to AIDS and progression to death after achieving a CD4 cell count of <200 cells/μL were much shorter for the HAART-era patients.

The probabilities of death after AIDS (P < .0001), AIDS after a CD4 cell count of <200 cells/μL (P = .0063), and death after a CD4 cell count of <200 cells/μL (P < .0001) diminished during the HAART era (figure 1). Median survival after AIDS increased from 29.8 months in the pre-HAART era to >70 months in the HAART era (P < .001). In the pre-HAART era, the median times to AIDS and to death after achieving a CD4 cell count of <200 cells/μL were 47.7 months and >120 months, respectively, and these times both increased to >130 months in the HAART era (P < .01 and P < .001, respectively).

As shown in table 3, factors associated with a higher relative risk of death after AIDS were male-male sex (MMS), a CD4 cell count of ≥200 cells/μL at the time of HIV diagnosis, and pre-HAART era. Male and pre-HAART-era patients were more likely to progress to AIDS after achieving a CD4 cell count of <200 cells/μL. Similarly, male sex, MMS, age of 50–59 years, and pre-HAART era were factors associated with a higher risk of death after a CD4 cell count of <200 cells/μL. Disease progression did not differ between Chinese and non-Chinese patients. Multivariate analysis revealed that treatment era was the only significant independent factor for death after the progression to AIDS and the most significant independent factor for the progression to AIDS or to death after a CD4 cell count of <200 cells/μL. Patients with advanced disease in the HAART era had a 62%–85% reduction in the risks of progression to death or to AIDS (table 4). Male sex, MMS, and age of ≥50 years were also independent variables associated with a higher risk of AIDS progression or death among patients who achieved a CD4 cell count of <200 cells/μL (table 4).

**DISCUSSION**

Survival among people in Western countries with HIV infection has improved since the introduction of HAART [8, 9]. In this study, we examined the progression to AIDS and to death among patients with advanced HIV-1 disease in the pre-HAART and HAART eras in Hong Kong. The HIV prevalence in our locality is low, and the dates of infection for most of the patients were unknown. We could not study disease progression since the time of HIV seroconversion because of the lack of such data in our patient cohort. On the other hand,
late HIV diagnosis was not uncommon in Hong Kong [10]. Moreover, morbidity and mortality associated with HIV infection are high among patients with advanced disease. It thus makes sense for us to concentrate on patients with advanced HIV disease: those with AIDS and/or a CD4 cell count of <200 cells/μL. Development of AIDS-defining illnesses clearly denotes advanced disease status. A CD4 cell count of <200 cells/μL is also a significant landmark in the course of HIV disease, because it prompts a heightened predisposition to major complications [11] and indicates the indisputable need for HAART initiation [12].

In the present study, survival among patients with AIDS and patients with a CD4 cell count of <200 cells/μL, as well as AIDS progression in the latter group, improved significantly in the HAART era. A positive health impact associated with the reduced numbers of patients who progressed to the clinical end points was uniformly evident, as revealed by the observed events, life-table analysis, and Cox proportional hazards model analysis. These findings echoed the benefits witnessed in North America [1, 2], Australia [13], and Europe [14] in recent years. Though somewhat not surprising, our study is among the few demonstrating the health impact of HAART in non-Western countries on a population level. Decreasing mortality and morbidity among patients with AIDS in Brazil [15] and Taiwan [16] have been reported elsewhere.

The median survival after progression to AIDS of 29.8 months in the pre-HAART era is higher than that found in previous studies [17, 18]. This may be related to our inclusion of patients treated through 1996 in the pre-HAART group, compared with an earlier cut-off year in these previous studies. To our knowledge, there were few reports on median survival duration after progression to AIDS in the HAART era. One Australian study reported a median survival duration of 39.6 months for patients with AIDS diagnosed in 1996–2000 [19]. Our finding of a median survival duration of 170 months during the HAART era would need to be confirmed by studies in other parts of the world. Multivariate analysis revealed that the risk of death for HAART-era patients decreased dramatically, by 85%, compared with the risk for pre-HAART-era patients (adjusted HR, 0.15; 95% CI, 0.08–0.26). It is conceivable that...
Table 4. Multivariate analysis of characteristics associated with progression to clinical end points of death after AIDS onset, progression to AIDS after achieving a CD4 cell count of <200 cells/μL, and death after achieving a CD4 cell count of <200 cells/μL for patients with advanced HIV-1 disease.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Death after AIDS</th>
<th>AIDS after a CD4 cell count &lt;200 cells/μL</th>
<th>Death after a CD4 cell count &lt;200 cells/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted</td>
<td>Adjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td>hazard ratio</td>
<td>hazard ratio</td>
<td>hazard ratio</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Female</td>
<td>...</td>
<td>1.00 (0.15–0.78)</td>
<td>...</td>
</tr>
<tr>
<td>HIV exposure category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td></td>
<td>1.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male-male sex</td>
<td></td>
<td>2.12 (1.44–3.11)</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1.60 (0.78–3.31)</td>
<td>...</td>
</tr>
<tr>
<td>Age at diagnosis of HIV disease, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–29</td>
<td></td>
<td>1.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30–39</td>
<td></td>
<td>1.43 (0.90–2.28)</td>
<td>...</td>
</tr>
<tr>
<td>40–49</td>
<td></td>
<td>1.48 (0.85–2.60)</td>
<td>...</td>
</tr>
<tr>
<td>50–59</td>
<td></td>
<td>3.75 (2.04–6.91)</td>
<td>...</td>
</tr>
<tr>
<td>&gt;60</td>
<td></td>
<td>3.61 (1.57–8.32)</td>
<td>...</td>
</tr>
<tr>
<td>Treatment era</td>
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<td>1.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-HAART</td>
<td>0.08–0.26</td>
<td>0.24–0.60</td>
<td>0.15–0.40</td>
</tr>
<tr>
<td>HAART</td>
<td>0.38</td>
<td>0.25</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a proportion of our patients could have continued to have their disease well-controlled with HAART beyond the date on which this study ended.

The improvement in the median time to progression to AIDS or to death among patients with a CD4 cell count of <200 cells/μL in the HAART era was less marked than the improvement in survival duration after progression to AIDS, a finding similar to that in another study [8]. Yet, compared with the pre-HAART era, the risk of AIDS and death in these severely immunosuppressed patients still decreased greatly by 62% (adjusted HR, 0.38; 95% CI, 0.24–0.60) and 75% (adjusted HR, 0.25; 95% CI, 0.15–0.40), respectively, during the HAART era. The finding of age as a risk for death even in HAART era among HIV-infected patients is consistent with a recent study [20]. We reckon that the 3 clinical end points employed in this study are useful indicators for assessing disease progression, and thus outcome, in patients with advanced HIV/AIDS. The inclusion of patients with a CD4 cell count of <200 cells/μL ensured that those with advanced immunosuppression due to HIV infection were not missed, because some of them may not develop AIDS-defining illness for a prolonged period. These indicators could be used to monitor and evaluate the health impact of increased HAART access throughout the world, as the expansion of HAART access is gradually implemented in the near future.

Patients in Hong Kong have had access to antiretroviral therapy for a long time, unlike patients in most other parts of Asia. When HAART becomes more widely available in less-developed Asian countries, health impacts similar to those observed in our study may be replicable after a few years of successful implementation of treatment programs. This notion is supported by the increasing number of studies that have recently demonstrated the efficacy of various HAART regimens in resource-limited settings [21, 22]. Our findings of substantial benefits in patients with advanced HIV disease provide useful data to assist resource-limited countries in planning the distribution of scarce antiretroviral treatment resources.

There are several limitations to our study that deserve attention. The biases inherent to observational studies apply to this study. The treatment history for the study population, including regimen and duration, was not available for analysis. Throughout the study, we followed Western recommendations on the use of antiretroviral therapy for treating our patients. However, it was most likely that some patients for whom antiretroviral treatment was indicated had not received it for various reasons, such as refusal or defaulted clinic follow-up. This could have happened for patients in both the pre-HAART and HAART eras. Given the proven benefits of HAART elsewhere, we felt that, in cases of undertreatment, our data would probably be biased toward an underrecognition of the observed impacts. Also, very low pretreatment CD4 cell counts [12, 23] and suboptimal drug adherence [24] could hamper the poten-
tial benefits of HAART. These confounding factors would again lead to an underestimation of the impact of HAART in the present study. Nevertheless, other confounding factors, such as improved diagnosis and treatment of opportunistic infections in recent years, might have resulted in an overestimation of the impact of HAART.

In our analysis, we also examined the effects of some known factors influencing progression to AIDS and death, including age [20, 25], CD4 cell count at the time of HIV diagnosis, and CD4 cell count at the time of AIDS diagnosis [26]. At a population level, we did not expect plasma viral load to deviate toward the high or low end at seroconversion in our patients, which would have affected disease progression [27]. Death is a definitive and ultimate end point of any disease, including HIV infection. Yet, we examined all-cause deaths and did not differentiate between deaths associated with HIV infection/AIDS and those due to other causes in our analysis. Moreover, the end points of death and AIDS alone may not be sensitive enough to delineate all major symptoms in HIV-infected patients.

In conclusion, we found that clinical outcome significantly improved for Hong Kong patients with advanced HIV-1 disease during the HAART era. Findings for survival and AIDS-free duration in this study may be relevant to the expected health impact associated with expanding HAART access in non-Western countries. Continual follow up and tracking of clinic cohort patients around the world would be useful in discerning the long-term efficacy and impacts of HAART.

Acknowledgments

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Conflict of interest. All authors: No conflict.

References

who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 × 10^4 cells/L. Ann Intern Med 2003;139:810–6.

