Trends in the prescription of antiretroviral drugs and impact on plasma HIV-RNA measurements

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Received 14 March 2008; returned 21 April 2008; revised 24 May 2008; accepted 26 May 2008

Background: The choice of antiretroviral drugs has evolved over the last decade. Recognition of trends and determinants of changes may help to make predictions on prescription patterns.

Methods: Longitudinal analyses were performed every 6 months from 1996 to 2006, of all HIV-infected individuals who attended at one HIV/AIDS referral centre located in Madrid, Spain.

Results: A total of 2602 different individuals attending during the study period were examined over 23 consecutive time-points. The number and proportion of patients under antiretroviral therapy significantly increased in the period 1996–99, with a plateau since then around 1100 patients, which represented around two-thirds of the patients seen at each time-point after the year 2000. The proportion of patients under antiretroviral therapy having undetectable viraemia significantly increased from 34.5% in 1996 to 80% in 2006. The relative use of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) has risen in recent years, while prescription of non-nucleoside reverse transcriptase inhibitors has declined compared with the period 1999–2001, when it peaked. Among NRTIs, the use of zalcitabine, stavudine and didanosine has dramatically declined or vanished, while zidovudine, lamivudine, abacavir and tenofovir have gained relevance. Among PIs, indinavir and nelfinavir have almost disappeared, being replaced by ritonavir-boosted PIs, mainly atazanavir and lopinavir. After its first introduction in the year 1999, efavirenz has been generally preferred over nevirapine.

Conclusions: The choice of antiretroviral drugs has evolved during the last decade, with safety and convenience issues driving most changes in prescription patterns, while antiviral success has dramatically increased.

Keywords: antiretroviral therapy, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors

Introduction

Antiretroviral treatment has been a major medical achievement which, in combination with antibiotic prophylaxis, has been estimated to have saved more than 3 million patient-years of life in the USA alone.1 Moreover, there is no doubt that the efficacy of antiretroviral therapy has increased over time. First, we learnt about the only transient benefit of mono- or bitherapy with nucleoside reverse transcriptase inhibitors (NRTIs), such as zidovudine,2 didanosine3 or zalcitabine.4 In 1996, the appearance of two new NRTIs, namely stavudine and lamivudine, and the marketing of protease inhibitors (PIs) as a new class of drugs gave birth to the concept of highly active antiretroviral therapy (HAART).5 For the first time, in patients under triple drug therapy, we assisted in dramatic CD4 count gains within months of treatment, with evidence of reduction in HIV replication below the limits of detection in most patients compliant with their medication. Altogether, these laboratory findings translated into remarkable reductions in morbidity and mortality in HIV-infected persons.6
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Although virologically effective, the clinical performance of initial PI-containing triple drug regimens was far from optimal, mainly due to frequent adverse events. The simplification of HAART first became possible in 1998 with the appearance of non-nucleoside reverse transcriptase inhibitors (NNRTIs). These new drugs proved at least as effective as PI when used along with two NRTIs. More recently, the co-formulation of different NRTIs in one pill and the boosting of PI with low doses of ritonavir have further enhanced the efficacy of HAART, as a result of improved convenience. There are currently 23 FDA-licensed compounds to treat HIV infection. The availability of new antiretroviral drugs and the increased knowledge of HIV disease have been accompanied by significant changes in antiretroviral prescription patterns. The aim of this study was to analyse the relative use of antiretroviral drugs, the factors influencing their prescription and the overall virological success of therapy over the last decade.

Methods

A retrospective review of antiretroviral drugs prescribed to HIV-infected patients was conducted at one AIDS/HIV referral centre located in Madrid, Spain. The assessment of drug prescription was made by 6 month consecutive cross-sections, specifically sampling patients every June and December, from December 1995 to December 2006. The total number of distinct HIV-infected patients, with or without antiretroviral drug treatment, attending at each time-point was recorded from the Pharmacy register and the clinic database.

Only adults older than 18 years with a positive serology (reactive EIA and confirmatory western blot) who had started or were already receiving antiretrovirals within the month of the analysis were included. Their main demographics, including age, gender and risk group, as well as plasma HIV-RNA values, were registered the first time each patient entered the database. The proportion of patients with plasma HIV-RNA <50 copies/mL (500 copies/mL before the year 2001) was determined at the closest time to each time-point, twice a year.

The choice of the antiretroviral regimen was at the discretion of the doctor in charge. Antiretrovirals had been always given free of charge at the hospital’s pharmacy, where each prescription was computerized into a central database, containing drugs and doses (dose per pill and per day), amount of tablets delivered and date of dispensing. As previously mentioned, it is the pharmacy policy to limit antiretroviral delivery to once per month, with a requirement for a new physician’s prescription form every 3 months. Therefore, all HIV-infected patients under antiretroviral therapy visited the pharmacy monthly or in the event of any unplanned treatment change.

Statistical analyses

All descriptive results are given as total numbers and percentages. Comparisons of percentages were made using the χ² test. All data were analysed using the SPSS v13.0 software (SPSS Inc., Chicago, IL, USA).

Results

From December 1995 to December 2006, a total of 23 cross-sectional analyses was performed. A total of 2602 different HIV-infected individuals on antiretroviral therapy was examined. Their main characteristics at the time of first inclusion in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2602</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>35 ± 7</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>68</td>
</tr>
<tr>
<td>Risk group (%)</td>
<td></td>
</tr>
<tr>
<td>injection drug user</td>
<td>52</td>
</tr>
<tr>
<td>homosexual men</td>
<td>39</td>
</tr>
<tr>
<td>heterosexual</td>
<td>7</td>
</tr>
<tr>
<td>others</td>
<td>2</td>
</tr>
<tr>
<td>CD4+ T lymphocytes (cells/mm³)</td>
<td>212 ± 246</td>
</tr>
<tr>
<td>Chronic hepatitis C (%)</td>
<td>32</td>
</tr>
</tbody>
</table>

The database are summarized in Table 1. There was a flux of patients who entered and left the HIV clinic during the study period due to a variety of reasons, including change of city or country of residence, deaths, voluntary transfer to other hospitals etc. On average, 190 new patients entered for follow-up per year and 40 stopped hospital visits. Overall, the mean number of patients on follow-up at different time-points in this 11 year study was 960 ± 143, ranging from a minimum of 275 patients in December 1995 to a maximum of 1190 in December 2005.

Figure 1 shows the evolution in the number of patients receiving antiretroviral treatment during the study period. There was a rapid increase in the rate of prescriptions up to mid-1999, while since year 2000 onwards the number of treated patients has remained fairly stable around 1100 patients. Among all HIV-infected individuals attending, the proportion under antiretroviral treatment increased from 37% in December 1996 to 55% in December 1998 (P < 0.001). From mid-1999 up to the end of the study, HAART has been given, on average, to 65% and 69% of all patients attending the outclinic. Figure 1 also shows the proportion of patients under antiretroviral treatment with undetectable plasma HIV-RNA during the study period. It should be highlighted that the proportion of treated patients with undetectable plasma viraemia steadily increased from 34.5% at the beginning of the study to up to ~80% at the end of the year 2006. A simple view might recognize two periods: before the year 2000, when the proportion of patients with undetectable plasma viraemia was not much beyond 60%, and since then, with a steady increase up to 80% at the end of the study period.

The relative contribution of NRTIs, NNRTIs and PIs to the total consumption of antiretrovirals during the study period is depicted in Figure 2. Drugs belonging to the NRTI family were the most prescribed medications at all time-points, in agreement with their role as the backbone of most HAART regimens. The prescription of PIs begun in 1996 and kept growing steadily up to June 1998, when NNRTIs started to be broadly used. The relative use of NNRTIs over PIs moved from 0.13 in June 1998 to 2.04 in June 2001, which means that by then NNRTIs were prescribed 2.04 times more than PIs. The relative use of NNRTIs began to decline by the end of 2004, when its prescription with respect to PIs was 0.98. This trend towards a lower use of NNRTIs over PIs has become more evident within the last few years, 0.79 being the relative use of these drugs by the end of 2006.
The prescription of different NRTIs along the study period is depicted in Figure 3. Zidovudine, didanosine and zalcitabine were the first antiretrovirals available. However, the prescription of zalcitabine was never >8% and lasted for a relatively short time, being almost absent by the end of 1998. The use of didanosine reached a maximum in 1996 (40% of treated patients), and a smaller second peak was seen in 2001 (20% of treated patients). Since then its prescription has steadily declined, being only 4% at the end of the study period.

The use of zidovudine, prescribed to more than half the patients at the beginning of the study, declined with the introduction of stavudine at the end of 1996. However, safety concerns (e.g. lipodystrophy, mitochondrial toxicity and lactic acidosis) caused a reduction in the prescription of stavudine from a peak of 40% in mid-1999 to <1% by December 2006. In contrast, zidovudine prescription has remained fairly stable over time, and even increased up to around 15% within the most recent years. It should be noted, however, that this was mainly driven by the availability of its co-formulation with lamivudine and/or abacavir. Tenofovir and emtricitabine are the most recent approved antiretroviral NRTIs, and are very often co-formulated in a single pill once a day. By the end of 2006, their prescription represented 16% of all NRTIs.

Figure 1. Number of patients on antiretroviral treatment and proportion of them with undetectable plasma HIV-RNA over time.

Figure 2. Trends in the relative prescription of antiretrovirals belonging to the three main drug families. NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.
The first available PIs back in 1996 were saquinavir, indinavir and ritonavir. While ritonavir prescription at full doses (600 mg twice daily) was rapidly abandoned, the use of indinavir and saquinavir declined more slowly (Figure 4) and in parallel with the introduction of NNRTIs. The availability of nelfinavir in 1997 was followed by a rapid decline in indinavir use, which moved from ~70% in 1996 to <20% when nelfinavir was at its maximum at the end of the year 2000. Lopinavir, co-formulated with low doses of ritonavir, was introduced in 2001 and rapidly displaced other PIs; by mid-2004, it represented ~80% of all PIs given. The availability of atazanavir during the last semester of 2004 was followed by a rapid switch in PI prescription patterns, mainly as a result of simplification strategies, and in an attempt to ameliorate lipid abnormalities and reduce the pill burden. The use of amprenavir was fairly low until mid-2005, but experienced an increase since then, when fosamprenavir became available. Finally, tipranavir was only marketed early in the year 2006, and it has mainly been prescribed to heavily antiretroviral-experienced patients. Its relatively poor safety profile and the need for it to be given along with 200 mg of ritonavir twice a day have limited its broader use. Only two NNRTIs, nevirapine and efavirenz, have been licensed in Spain. Figure 5 shows trends in their respective prescription. Nevirapine was first introduced in June 1998, and efavirenz, a year later. Prescription of both NNRTIs has remained balanced over time, with a slight trend towards increased use of efavirenz.

**Discussion**

The achievement of an effective treatment for HIV infection has been one of the most remarkable milestones in the recent history of medicine. This is true not only for the number of lives that have been saved, but also for the amount of scientific
information that has been generated alongside the daily treatment of HIV-infected individuals. The analysis of changes in the prescription of antiretroviral drugs is a good exercise of how clinical practice and research may meet to continuously improve the management of HIV-infected patients. Here, we describe the evolution of prescription patterns of antiretroviral medications during the first 11 years of the HAART era. Although similar studies have been conducted by others, this is the longest, and has a large population.

At the beginning of the HAART era, and somewhat under the influence of the attractive paradigm ‘hit hard, hit early’, most patients were put under treatment regardless of immune status, in view of the rapid suppression of HIV replication achieved in most cases. This was accompanied by a sharp decline in AIDS-related morbidity and mortality in the Western world. Both factors, treatment efficacy and physicians’ readiness to start therapy, explain the rapid increase in antiretroviral drug prescriptions observed at our institution between 1996 and 2000.

The initial enthusiasm generated by HAART success was somewhat blunted in the following 2–3 years for three main reasons. First, the awareness that HIV eradication was not feasible despite long-term suppression of viral replication. Second, the recognition of a significant impairment in the patient’s quality of life as a result of adverse effects and high pill burden of the medication. Lastly, the relatively frequent occurrence of drug resistance in the event of viral breakthrough. As a result, there was a progressive trend towards delayed initiation of HAART. This fact translated, in our clinic, into a slow-down in HAART exposure since 1998, which plateaued in mid-2000 to around 1100 patients. This figure has remained fairly stable up to December 2006. A similar trend in HAART prescription has been reported by others.

As expected, the proportion of patients with undetectable plasma viraemia grew in parallel with the number of treated patients. By the end of 1999, however, it stabilized to around 60% of patients under HAART. This figure, on the other hand, may indirectly reflect the accumulation of patients who had failed NNRTI and the first PI generation. The wide prescription of NNRTIs as part of first-line therapy and ritonavir-boosted second-generation PIs since mid-1998 was the main factor explaining the regain of an increased efficacy of HAART since then. By the end of the study period, the rate of virological success increased up to 80% of all treated patients. The availability of easier-to-take forms of NRTI medications, including co-formulations, and the movement to once-daily dosing have been other important determinants of this enhanced HAART efficacy over time. All these factors, along with the recommended use of two NRTIs as the backbone in most HAART regimens, explain why, as a whole, 70% of all prescribed antiretroviral medications belong to the NRTI family.

The results of our study show that three major forces have driven the prescription of different antiretrovirals in the last decade, namely efficacy, safety profile and simpler administration. There is little doubt that lack of efficacy accounted for the disappearance of zalcitabine and that toxicity issues explained the rapid decline in stavudine use. In contrast, zidovudine and lamivudine regained positions after 2001, when a co-formulation became available. Tenofovir and emtricitabine were the latest NRTIs to enter the market, but they have rapidly gained positions, most likely due to a combination of good tolerance, convenience and potency.

It should be noted that no more than 15% of all antiretroviral medications prescribed since 2002 were PIs. These drugs were rapidly incorporated into the HIV armamentarium in 1996, once their efficacy in combination with NRTIs was proven. However, as noticed by others, the overall use of PIs began to decline as early as in 1998, when NNRTIs first became available, and when the first reports of the lipodystrophy syndrome appeared. All first-generation PIs, namely indinavir, saquinavir, ritonavir and even nelfinavir, are now seldom used. These drugs have been replaced by novel PI
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compounds, such as lopinavir, atazanavir and tipranavir which, when boosted with low doses of ritonavir, are more effective and convenient.

The introduction of the first NNRTI occurred in 1998. Enhanced convenience and lack of metabolic side effects drove the switching of strategies from PI to NNRTI. The use of NNRTIs has relatively declined over time, given its low genetic barrier for resistance and cross-resistance. Their use has been mainly restricted to first-line therapies in recent years. The use of either nevirapine or efavirenz has been well balanced over time at our clinic with a trend towards increased prescription of efavirenz over nevirapine, in agreement with the slight advantage seen in some clinical trials, and by the fact that a relatively high proportion of our patient population had chronic hepatitis C, a condition that may be prone to development of hepatotoxicity using nevirapine.

Some limitations of our study should be acknowledged. The analysis of the prescription of antiretrovirals was performed in an open cohort, in which we had no information regarding the specific number of patients periodically entering or exiting. Most likely, prescription patterns would have been fairly different if drug-naive and treatment-experienced patients could have been considered separately, or if plasma HIV-RNA levels and/or CD4 counts had been taken into account. On the other hand, treatment changes occurring within a period shorter than 6 months may have been missed, causing underreporting of the use of drugs with very early toxicity profiles, such as abacavir, nevirapine or efavirenz. Finally, no assessment of associations between distinct antiretrovirals was made, which would have helped to better appreciate the reasons for some changes in prescription patterns.

In summary, despite a relative stabilization in the number of patients under HAART seen at our institution since year 2000, there has been a steady increase in the proportion of treated patients with undetectable plasma HIV-RNA. The simplification of HAART regimens, by using antiretrovirals with simpler schedules and improved tolerability, together with enhanced potency, are good reasons to explain this observation. Convenience, safety and potency are the three major forces that drive antiretroviral prescription patterns in the clinical setting.

Funding

This work was supported in part by grants from Fundación Investigación y Educacion en SIDA (IES), Agencia Lain Entralgo, the European AIDS Treatment Network (NEAT) and the Spanish AIDS Network (ISCHI-RETIC RD06).

Transparency declarations

None to declare.

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