

ORIGINAL RESEARCH

Patterns of antiretroviral use in the United States of America: analysis of three observational databases

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Objective

To characterize patterns of antiretroviral use in HIV-infected patients and explore variation by patient characteristics and disease stage.

Methods

Three large patient databases recording information derived from routine clinical attendance were analyzed: HIV Insight ($n = 10\,873$), Target Management Services ($n = 2226$) and Clinical Partners ($n = 1505$). Each database records the dates of starting and stopping individual antiretroviral agents over time, measurements of CD4 T-cell counts and HIV-RNA levels at approximately 6-monthly intervals, and the demographic characteristics of patients. The number, frequency and duration of different antiretroviral combinations over time and their relationship to stage of HIV-disease and demographic characteristics were explored.

Results

Over 2000 different combinations of antiretroviral agents are recorded. From 1987 onwards, the use of zidovudine increased, with 23% of patients receiving monotherapy by 1990. The majority of treated patients remained on monotherapy until the introduction of highly active antiretroviral therapy (HAART) in 1996. By 1999, the standard of care was HAART, with 84% of patients beginning antiretroviral therapy with HAART. Those of African American race (odds ratio 0.59) and funded by Medicaid (odds ratio 0.72) were significantly less likely to begin antiretroviral therapy on HAART. Until 1995, there was a significant decrease in CD4 T-cell count when starting antiretroviral therapy. No significant trend was observed in either CD4 T-cell count or viral load after this time. Those starting on HAART therapies were significantly less likely to stop or switch regimens than those on nucleoside reverse transcriptase inhibitor (NRTI)-only therapies ($P < 0.001$).

Conclusions

Complex patterns of antiretroviral treatment are observed in this large population. Changes over time mirror the introduction of the new antiretroviral agents.

Keywords: antiretroviral therapy, HIV, observational database

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Introduction

Antiretroviral therapy for HIV infection first became available in the late 1980s, with the licensing of the nucleoside reverse transcriptase inhibitor (NRTI), zidovudine [1–3]. This remained the mainstay of antiretroviral therapy for many years, until the introduction of a number of other RTIs, including didanosine, lamivudine and stavudine [1, 4–7]. However, the major changes to antiretroviral therapy arose from 1996 onwards with the emergence of a new class of compounds [protease inhibitors (PI)] and the introduction of therapies incorporating combinations of drug classes [8–10]. The licensing of other drug classes, in particular nonnucleoside reverse transcriptase inhibitors (NNRTI) [11, 12], has led to a wide range of possible different antiretroviral agents and therapy combinations. There are now 18 individual drugs licensed for use in the USA, with many different possible therapy combinations in frequent use [1].

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These new combinations, often referred to as HAART therapies (highly active antiretroviral therapies), have been shown to have a dramatic impact both on markers of disease progression (viral load and CD4 T-cell counts) [8–14] and on HIV-associated mortality and morbidity [15–20]. National guidelines for the treatment of HIV infection in both the USA and other European countries therefore recommend HAART therapies (either one PI or one NNRTI plus two NRTIs) as first-choice therapy [21].

Aside from the marketing data collected by pharmaceutical companies, information on the ways in which individual antiretroviral drugs and combinations are used in treating HIV infection, and at what stage of infection treatment is initiated, is generally derived from reports from individual clinic settings. Furthermore, many of the studies published focus on research-based cohorts or clinics [22–30], where patterns of antiretroviral use may be very different from those in other less well-researched populations. Large-scale detailed patterns of antiretroviral use have therefore only been reported by a few cohort studies, such as the Multicentre AIDS cohort study [31, 32] and the EUROSIDA project [22]. While such cohorts provide a representative picture of the population under study, treatment patterns in clinics participating in these research-based studies may differ from those prescribed in the general population or in smaller clinics. Knowledge of these trends provides useful information both for those involved in healthcare planning and for individual practitioners. In particular, such research is important in identifying differences in standards of care in different groups, so that resources can be focused on those receiving poorer care.

The purpose of this paper is to provide a picture of antiretroviral use in the general HIV-infected population in the USA, through analysis of data collated from three large HIV patient databases. These databases provide information on the patterns of use of approximately 14 000 patients who were prescribed antiretroviral therapy from 1986 onwards. While such observational data cannot be considered 'representative' of the population as a whole (as they are not population-based samples), they provide a rich source of information on the patterns of antiretroviral therapy in use by a large number of HIV-infected individuals from a variety of different clinical settings.

Methods

Data

Data were analyzed from three large HIV patient databases, HIV Insight™ (APACHE), Target Management Services (TMS) and Clinical Partners (CP), all of which record information obtained during routine clinical practice in a group of clinics on patients with HIV infection in the United States. The patients in the TMS database attended clinics in New York, New Jersey or Los Angeles. The location within the USA of clinics was not disclosed for the CP and APACHE patients, but cover a variety of locations. No restriction is placed on entry into the database – all patients attending one of the participating clinics over the time course of the study are therefore included in the database. In particular, the databases include patients funded by a variety of sources, including private insurance, Medicare and Medicaid. The information recorded in the databases is entered at each clinic visit from clinical notes according to the protocols of the individual clinics, and recorded in a standardized form. Internal consistency checks are made on the reliability of the data at this stage. While there are differences in the format and recording of the information between the three databases, several aspects of the data are collected routinely in all three datasets. Thus, each database records the demographics of the patients (including gender, age and risk group), a complete record of each antiretroviral drug taken with starting and stopping dates, and CD4/CD8 T-cell counts and viral load measurements taken at each visit to the clinic (typically between two and four times a year). The maximum lower limit of detection for viral load measurements was 400 HIV-1 RNA copies/mL for TMS and CP and 500 copies/mL for APACHE. In addition, the APACHE database records additional information on race, insurance status and education level.

The APACHE database records information on 10 873 patients enrolled from 1983 onwards, TMS on 2226 patients enrolled from 1986 onwards and CP on 1505 patients enrolled from 1988 onwards, giving a total population size of 14 604 patients in the combined database. The median duration of follow-up for each patient was 1 years 8 months in APACHE, 4 years 1 month in TMS and 2 years 9 months in CP. Date of death is not known for any TMS or CP patients and is known for less than 5% of the APACHE patients recorded as 'inactive' within the APACHE database.

To exclude potential data entry errors in the recording of therapy, patients were excluded from the analysis if any of the individual antiretroviral agents was recorded more than 2 years prior to FDA approval of the agent (to allow for inclusion of patients in clinical trials). This resulted in the exclusion of 450 patients in APACHE, 433 patients in TMS and 26 patients in CP. The patients analyzed are classified by year of enrolment in the database (Table 1). Only 44% of patients in the APACHE database were enrolled since 1996, compared with 74% and 84% in TMS and CP, respectively. However, due to the relative sample sizes, the majority of patients (64%) recruited since 1996 are enrolled in the APACHE database.

Table 1 Number of patients analyzed by year of enrolment in one of three databases

Before 1989	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
147	253	412	464	832	1195	1512	1696	2548	1818	1412	919	487

Statistical analysis

Individual drugs were combined to evaluate a combination therapy for each patient each time an individual drug was changed. The pattern of first antiretroviral therapy was explored over time, by CD4 T-cell count, by viral load and by risk group. The pattern of overall antiretroviral usage was examined over time by taking the combination therapy used by each patient every year. Due to the small number of observations early on, this was started from 1 January 1988. Combination therapies were classified into NRTI monotherapy, NRTI dual-therapy and HAART therapies (PI-and/or NNRTI-containing). Trends in CD4 T-cell counts and log-transformed viral load over time were assessed using linear regression. For CD4 T-cell counts two trends were tested: a linear trend prior to 1996 and a linear trend from 1996 onwards.

First antiretroviral therapy was further classified into HAART (PI-and/or NNRTI-containing therapy) and NRTI-only. Univariate differences in first antiretroviral therapy by demographic and social characteristics (gender, age, race, risk group, insurance status and education level) were assessed using χ^2 tests. Logistic regression was performed to assess the demographic and social characteristics determining first antiretroviral therapy, adjusting for the calendar year of starting therapy. These analyses were restricted to the APACHE database, as the other databases do not record detailed information on all of these characteristics (see Table 2). All analyses were undertaken using SAS Version 6.12 [33].

The duration of first antiretroviral therapy was compared for different therapies using Kaplan–Meier curves and proportional hazards models [34], adjusting for differences in calendar year. The proportional hazards assumption was checked by examination of the residuals. The duration of first therapy was analyzed by therapy class (HAART or NRTI-only). Patients were considered to have remained on their first therapy if they changed individual drugs within the regimen but did not change their therapy class.

Results

Table 2 summarizes the demographic and social characteristics of the patients included in the analysis. No significant differences were observed between TMS and CP in the age of the patients. However, patients in APACHE were on average 1.6 years younger ($P < 0.001$). The majority of the sample is male with homosexual risk group. The CP database appears to have more patients from the IVDU and heterosexual risk groups. However, risk group was not recorded for approximately two-thirds of this dataset, and the similarity in the percentage of male patients in all three databases suggests that the homosexual risk group may have been underreported in the CP database.

The first antiretroviral agent, zidovudine, received Food and Drug Administration (FDA) approval for treatment of HIV-infected individuals in 1987. Four other antiretroviral agents received approval shortly afterwards. From 1987 onwards, the total use of these NRTIs increased exponentially in this population (Fig. 1a), peaking in 1997. Interestingly, the use of three key NRTIs, zidovudine, lamivudine and

Table 2 Demographic and social characteristics of patients in the three databases

	APACHE	TMS	Clinical partners
Number of patients	10 423	1793	1479
Male (%)	8965 (86%)	1499 (84%)	1226 (83%)
Mean age (years)	36.9	38.3	38.7
Risk group (%)			
Homosexual	6989 (72%)	915 (61%)	96 (28%)
IVDU	1172 (12%)	231 (15%)	111 (33%)
Heterosexual	1368 (14%)	280 (19%)	132 (38%)
Other	159 (2%)	81 (5%)	3 (1%)
Not recorded	735	286	1137
Race (%)			
White	6359 (61%)	–	–
Hispanic	989 (9%)	–	–
African American	2718 (26%)	–	–
Other	215 (2%)	–	–
Not recorded	142 (1%)	–	–
Education			
Less than high school	894 (9%)	–	–
High School	1620 (16%)	–	–
College	4699 (45%)	–	–
Not recorded	3210 (30%)	–	–
Insurance			
Private/self-pay	3337 (32%)	–	–
Medicare	911 (9%)	–	–
Medicaid	2068 (20%)	–	–
Other*	3804 (36%)	–	–
Not recorded	303 (3%)	–	–

*Includes PPO, HMO, Point of Service, Ryan White/ADAP and Clinical Study.

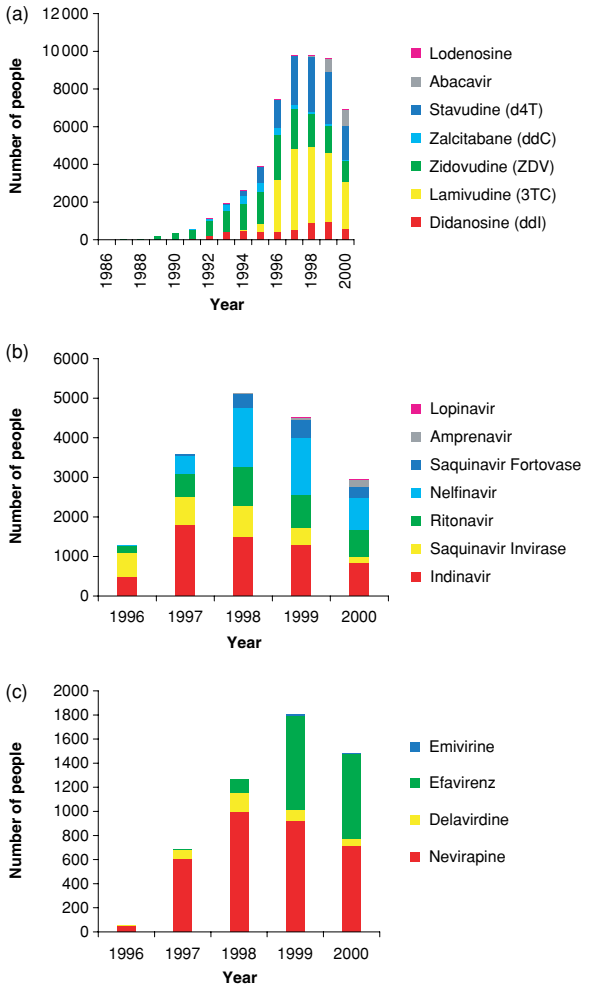

Fig. 1 Number of patients using each antiretroviral agent at the beginning of each calendar year. (a) NRTIs; (b) PIs; and (c) NNRTIs.

zalcitabane, dropped in this population from 1996 onwards, the time at which new classes of antiretroviral agents were introduced. The use of three other NRTIs, stavudine, didanosine and abacavir increased from this time onwards, perhaps reflecting a change in choice of NRTIs in combination therapy.

PIs were first introduced in 1996, following FDA approval of saquinavir, ritonavir and indinavir in late 1995. The use of these agents increased rapidly (Fig. 1b). The use of indinavir declined from 1997 onwards, while the use of nelfinavir increased. The use of saquinavir hard-gel formulation dropped dramatically with the introduction of the soft-gel compound, although approximately 500 individuals are still recorded taking the hard-gel formulation in 1999 (with two-thirds of these taking ritonavir simultaneously). There appears to be a decline in the overall use of PIs from 1998 to 1999, concurrent with the introduction of NNRTIs. Use of NNRTIs became widespread in 1997 with the licensing of nevirapine, with their use now equally split in this population between nevirapine and the more recent drug, efavirenz.

A large number of different drug combinations are theoretically possible from the 18 antiretroviral agents currently approved for use. For example, from the 18 drugs there are theoretically 4896 ways to choose a triple-therapy, 306 ways to choose a dual-therapy and 18 ways to choose a monotherapy, giving a possible total of 5220 combinations. In practice there will be a more limited number of combinations due to the composition of combinations within different drug categories (NRTI/NNRTI/PI), cross-reactions between drugs and, more recently, the marketing of combined products. However, over 2000 different combinations of the 18 antiretroviral agents are recorded in the database, reflecting the great diversity of different antiretroviral therapies now available. 155 of these combinations are recorded frequently, with over 10 000 patient-days of use.

Figure 2(a) shows the overall pattern of antiretroviral combinations in use at the beginning of the calendar year. Following the introduction of zidovudine in 1987, the proportion of patients receiving antiretroviral monotherapy continued to rise, reaching 23% in 1990. At this time, RTI dual-therapy became available, although the majority of treated patients in this database remained on monotherapy. The introduction of HAART in 1996 coincided with a significant further increase in the proportion of patients treated ($P < 0.001$), with more than 70% of patients receiving some form of antiretroviral therapy since 1996. The majority of patients currently take either a PI-and/or NNRTI-containing regimen.

Figure 2(b) shows the choice of initial antiretroviral therapy over time. From 1986 to 1994, initial antiretroviral therapy was predominantly NRTI monotherapy, with 80% of those beginning therapy in 1994 starting on such a regimen. The introduction of HAART in 1996 dramatically altered initial therapy patterns, with only 6% of patients beginning on NRTI monotherapy by 1997. USA guidelines now recommend HAART therapies for first-line antiretroviral therapy. However, even in 1999, a substantial number of patients (16%) began what is now considered to be suboptimal therapy, either NRTI monotherapy (6%) or NRTI dual-therapy (10%). These percentages did not differ for men and women ($P = 0.83$), but they did differ by database ($P < 0.001$) with 93%, 86% and 78% of CP, APACHE and TMS patients, respectively, receiving HAART as their first antiretroviral therapy in 1999.

Figure 2(c) shows the baseline measurements of CD4 T-cell count and, from 1990 onwards, HIV-1 RNA levels when commencing antiretroviral therapy. No significant

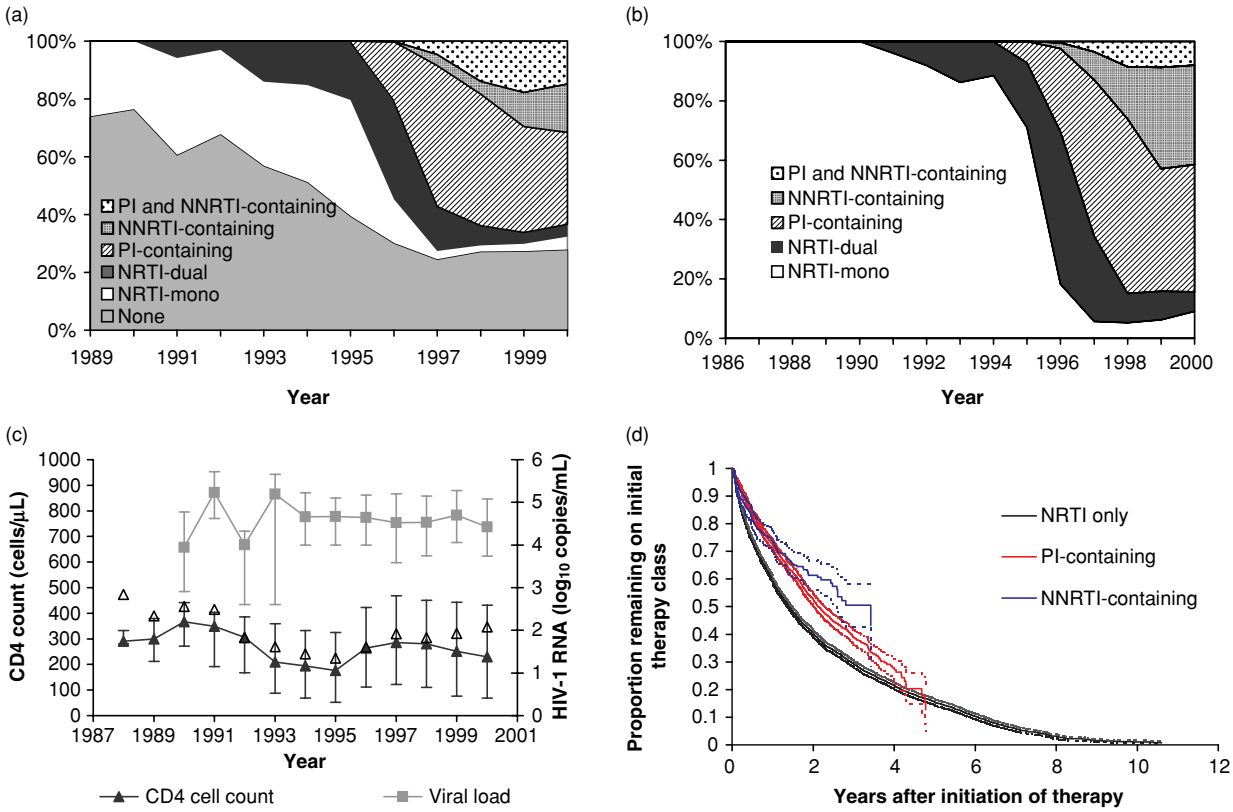

Fig. 2 (a) Pattern of antiretroviral regimens in use by calendar year. (b) Initial antiretroviral regimen on commencing therapy by calendar year. (c) CD4 T-cell count (cells/μL) and viral load measurements (log10 copies/mL) when commencing antiretroviral therapy (median and interquartile range) by calendar time (▲ and ■, respectively) with median CD4 T-cell count at first CD4 measurement (cells/μL) (open triangle); (d) Kaplan–Meier curve for the duration of first antiretroviral therapy.

trend was observed in viral load measurements or CD4 T-cell counts from 1996 onwards ($P = 0.13$ and 0.10, respectively). However, a significant decrease in CD4 T-cell count at initiating therapy was observed prior to 1996 ($P < 0.001$). In 1999, at starting therapy, the median CD4 T-cell count was 230 cells/μL, consistent with current guidelines, which recommend commencing treatment at < 500 cells/μL [21].

Significant differences in first antiretroviral therapy were observed based on demographic characteristics of those in the APACHE database. In univariate analyses, gender (men more likely to receive HAART, $P = 0.025$), age (odds of receiving HAART increasing linearly with age, $P < 0.001$), risk group (heterosexuals more likely to receive HAART, $P < 0.001$), race (white patients less likely to receive HAART, $P < 0.001$), education level (college-educated patients less likely to receive HAART, $P < 0.001$) and insurance status (private/self-pay patients less likely to receive HAART, $P < 0.001$) were associated with whether or not HAART was prescribed as the first therapy. However, the patterns of association are likely to be correlated with the calendar year of prescribing. In a logistic regression analysis adjusting linearly for age and calendar year of starting antiretroviral therapy, men and heterosexuals are more likely to receive HAART as first antiretroviral therapy, whereas African Americans and those whose treatment is funded by Medicaid were less likely to receive HAART as first antiretroviral therapy (Table 3).

Figure 2(d) shows the Kaplan–Meier survival curve for the duration of first antiretroviral therapy. The median duration of therapy was 1.5 years for those on NRTI-only therapy, 2.25 years for those on PI-containing therapy and 2.8 years for those on NNRTI-containing therapy. Those on HAART regimens (PI-and/or NNRTI-containing) were significantly less likely to stop or switch therapy than those on NRTI-only regimens ($P < 0.001$). In a hazards model, this difference remained significant ($P < 0.001$) after adjusting for calendar year of starting therapy.

Figure 3 shows the pattern of switching regimens for the first three regimens. Because of the complex patterns of individual regimens recorded in the dataset, we have presented this switching by regimen class only. For patients beginning NRTI monotherapy (40% of the population),

Table 3 Demographic and social characteristics determining first antiretroviral therapy. HAART is defined as a PI-and/or NNRTI-containing regimen. The analysis was restricted to the APACHE database since this is the only database recording these detailed characteristics

n = 8312	Odds ratio	95% Confidence interval	*P*
Calendar year	3.4	(3.2, 3.6)	< 0.001
Age (in years)	1.0	(1.0, 1.0)	0.30
Gender			
Female	1.0	–	–
Male	1.3	(1.0, 1.7)	0.04
Risk group			
Homosexual/bisexual	1.0	–	–
IVDU	1.0	(0.78, 1.3)	0.89
Heterosexual	1.3	(1.0, 1.7)	0.02
Other	1.3	(0.69, 2.4)	0.41
Not recorded	1.6	(1.1, 2.5)	0.02
Race			
White	1.0	–	–
Hispanic	0.80	(0.62, 1.0)	0.08
African American	0.59	(0.50, 0.71)	< 0.001
Other	0.61	(0.36, 1.0)	0.06
Not recorded	1.3	(0.52, 3.0)	0.61
Education			
Less than high school	1.0	(0.76, 1.3)	0.99
High School	0.89	(0.71, 1.1)	0.32
College	1.0	–	–
Not recorded	1.3	(1.1, 1.6)	< 0.001
Insurance			
Private/self-pay	1.0	–	–
Medicare	0.95	(0.72, 1.3)	0.72
Medicaid	0.72	(0.56, 0.92)	0.01
Other*	0.90	(0.75, 1.1)	0.29
Not recorded	1.3	(0.64, 2.7)	0.46

*Includes PPO, HMO, Point of Service, Ryan White/ADAP and Clinical Study.

only 19% remained on this type of regimen. Half of this group switched to NRTI dual-therapy, with 45% of this population switching later to a HAART therapy. Virtually all of the patients who stopped therapy (21%) re-started some class of therapy, most often monotherapy. Twenty-four percent of the population began on NRTI dual-therapy. Half of these (54%) later switched to a HAART therapy, with 27% remaining on NRTI dual-therapy. Again, virtually all of the patients who stopped therapy re-started at some point. Thirty-six percent of patients started on a HAART therapy. The majority of these patients (78%) have remained on this class of therapy. The remainder mostly stopped therapy (15%), with the majority of these patients (89%) re-commencing HAART therapy at a later date.

Discussion

In this study, we have documented patterns of antiretroviral use in three large databases of HIV patients attending for treatment in the USA. While one cannot ensure that this dataset is representative of the population as a whole, it provides a good description of practices in a diverse population of patients. In 1999, the majority of patients in this dataset were receiving HAART regimens, consistent with current guidelines for HIV treatment. However, a minority continue to receive what are now considered to be suboptimal treatments. As observed in other studies [27–31], there were significant differences in the standard-of-care received by gender, risk group, race and insurance status, with men and heterosexuals more likely to receive HAART as first antiretroviral therapy and those of African American race and those insured under Medicaid less likely to receive HAART as first antiretroviral therapy. These differences highlight the need for specific interventions to ensure equal access and standards of care in different subpopulations. Unfortunately, similar data were not available for the CP and TMS databases to allow the between-database differences to be explained by differences in patient demographics.

Past use of antiretrovirals in this population mirror the availability of the different antiretroviral agents. Following the licensing of zidovudine in 1987, the proportion of patients receiving monotherapy continued to rise, peaking in 1990. Although NRTI dual-therapy became available and was recommended by key clinical trials in the early 1990s [5–7], the majority of this population remained on monotherapy. The key changes in treatment patterns arose in 1996 with the introduction of PIs and NNRTIs. The first publications documenting the increased efficacy of these agents in combination with NRTIs (HAART therapy) appeared in 1996 [8], and resulted in an increase in the proportion of patients receiving some form of antiretroviral treatment to more than 70% since 1996. Prior to the introduction of HAART in 1996, there was a significant trend towards starting therapy at a later stage of infection (as measured by baseline CD4 T-cell count). After this time, no significant trend was observed in either CD4 T-cell count or viral load. However, there were differences in the duration that patients remained on their first antiretroviral therapy, with those on HAART therapies significantly less likely to stop or switch regimens than those on NRTI-only therapies. This result is in part due to the switching to HAART regimens observed in those on NRTI monotherapy and dual-therapy, which occurred with the introduction of these new regimens.

Perhaps the most important observation that arises from analysis of this dataset is the great heterogeneity in both the duration and combination of individual antiretroviral agents currently in use. Our results showed that over 2000 different combinations of the 18 licensed antiretroviral agents have been used, with hundreds of these combinations represented frequently in the database. This large number of combinations represents only part of the complexity of current treatment patterns. Each individual patient

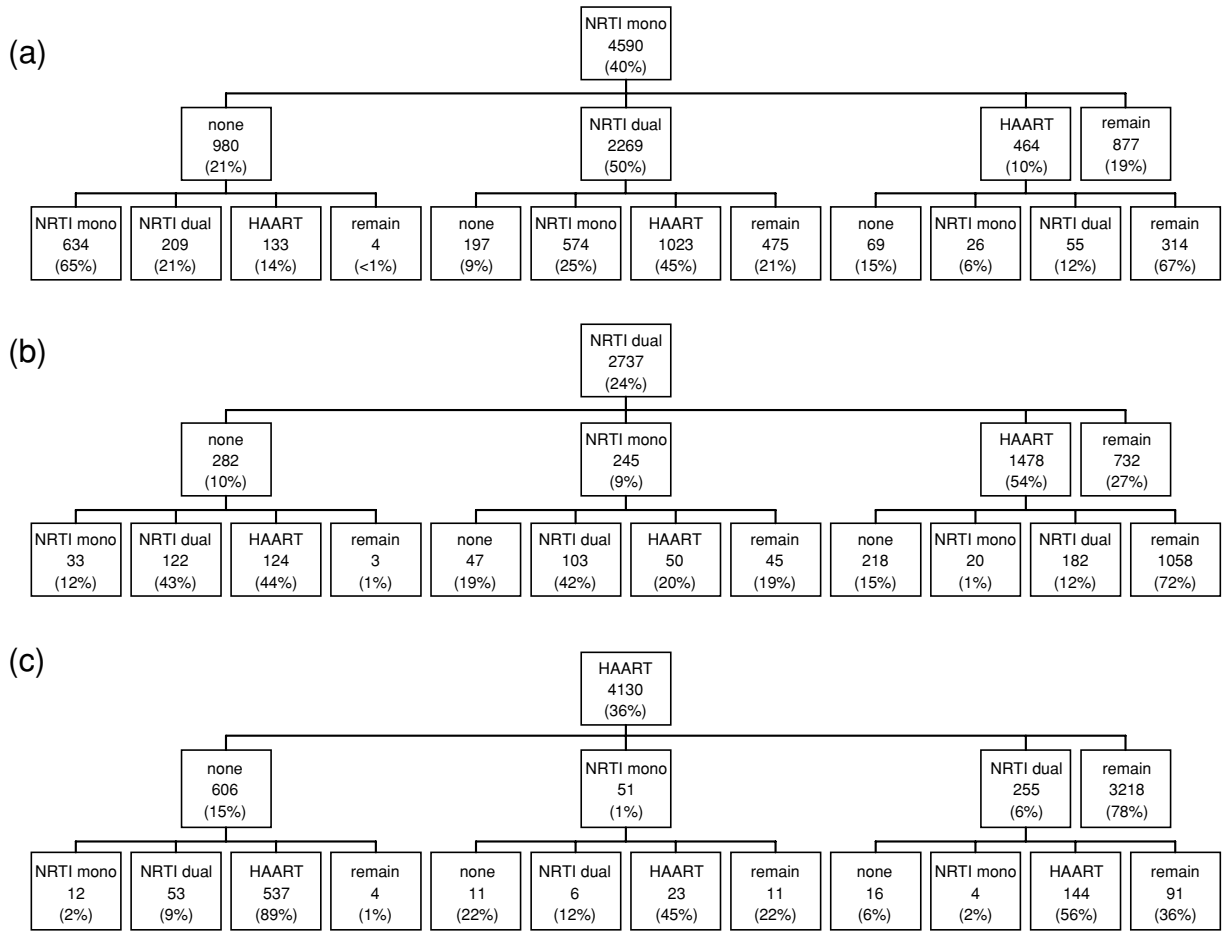

Fig. 3 Patterns of switching therapy. The top cell denotes the initial therapy class. The second row denotes the first switch and the third row the second switch. (a) Begin RTI monotherapy; (b) begin RTI dual-therapy; (c) begin HAART.
NRTI, nucleoside reverse transcriptase inhibitor; HAART, highly active antiretroviral therapy.

will begin and change therapies over the course of their treatment for a variety of reasons. Thus the number of patterns of treatment regimens, when these changes are included, is much greater than the number of antiretroviral combinations alone.

This great heterogeneity in treatment patterns poses considerable challenges for the evaluation of therapy success. While in the past, most diseases have been treated with a single agent, the effectiveness of which is evaluated in clinical trials, it is more difficult to evaluate HIV treatment under such gold standards. The number of different treatment combinations and patterns greatly exceeds those that have been examined in clinical trials. Furthermore, clinical trials are also limited to relatively short follow-up, typically 48 weeks. Clinical databases will therefore provide an opportunity to evaluate the complex patterns of antiretroviral treatment that are currently in use. While the data provided by observational databases are certainly not ideal (particularly since treatments are not randomly assigned), they may provide important additional information on the relative effectiveness of different treatments if analyzed carefully [35, 36]. Evaluation of the complex treatment patterns observed will require very large numbers of patients and good follow-up of these patients, and hence will be most successful if individual clinical datasets are combined into large-scale databases.

Findings on clinical outcome from observational studies should be compared with those obtained in randomized clinical trials whenever possible [37]. If findings are inconsistent, then there may be a selection bias in the observational data that was not fully controlled for in the analysis. However, observational studies such as this provide insights into treatment allocation patterns, such as African-American patients being less likely to start with HAART, that cannot, by definition, be estimated using clinical trial data. Thus, both types of study can make important contributions to gaining the most accurate picture possible of the current treatment of HIV-infected patients.

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