Evolution of Antiretroviral Prescription and Response over a Period of 8 years: an Italian Multicentre Observational Prospective Cohort Study

L. Sighinolfi, C. Torti, C. Zeni, F. Ghinelli, F. Suter, F. Maggiolo, A. Antinori, G. Antonucci, F. Castelnuovo, N. Ladisa, M. Migliorino, S. Novati, A. De Luca, S. Lo Caputo, G. Paraninfo, C. Tinelli, G. Carosi, and the Italian MASTER Database Cohort

Abstract

Background: There is very less information on the use of antiretroviral (ARV) drugs and viro-immunological outcome over calendar years in Italy.

Patients and Methods: We performed an analysis of a prospective observational cohort (MASTER) to assess antiretroviral drug use in first line HAART and explore whether initial treatment response changed over the years.

Results: 3,648 ARV-naive patients with available HIV-RNA and CD4+ T cell count at baseline who started their first HAART between 1997 and 2004 were studied. Mean age was 37.7 years; they were mostly males (72.3%) and Italians (81.4%). Prescription of non-nucleoside reverse transcriptase inhibitors and protease inhibitors boosted with ritonavir rose from 0.3% in 1997 to 58% in 2004 and from 0.3% in 1997 to 33.4% in 2004, respectively. Virological failures decreased over calendar years: from 42.9% in 1997 to 8.1% in 2004 after 6 months of HAART ($p < 0.001$); from 42.1% (1997) to 10.7% (2004) after 12 months ($p < 0.001$) and; from 39.5% (1997) to 8.2% (2004) after 18 months ($p < 0.001$). The same trend, but less striking, was found for immunological failure rates.

Conclusions: In the general Italian population of HIV-positive patients, evolution of treatment prescription correlated with improved viro-immunological outcome.

Infection 2008; 36: 244–249
DOI 10.1007/s15010-007-7227-0

Introduction

The introduction of highly active antiretroviral therapy (HAART) resulted in a decline of HIV-associated morbidity and mortality, thus transforming the HIV infection into a chronic condition [1–4]. Planning for long-term success is of overwhelming importance, keeping in mind that the first HAART regimen is the best chance for long-term success [3].

The characteristics of first line HAART changed over the years depending on the evolution of treatment guidelines, availability of new drugs, results of clinical trials and observational studies. Randomized clinical trials (RCT) demonstrated that rates of failures are low with the new regimens [5–7]. However, there are important gaps between RCT and the clinical practice. For instance, different characteristics of patients (such as higher proportions of patients with hepatitis co-infections or co-morbidities in real life), and different standards of clinical care may cause discrepancies between RCT and the results from observational cohorts.

This study was aimed at exploring whether short-term viro-immunological response to first line HAART improved in Italy and as to the factors that may have influenced such a trend.

L. Sighinolfi, F. Ghinelli
A.O. Sant'Anna, Ferrara, Italy
C. Torti *(corresponding author)*, **C. Zeni, G. Paraninfo, G. Carosi**
Institute of Infectious and Tropical Diseases, Università degli studi, University of Brescia, School of Medicine, P.le Spedali Civili, 1, 25123 Brescia, Italy; Phone: (+39/030) 399 6624, Fax: 303061, e-mail: torti.carlo@libero.it
F. Suter, F. Maggiolo
Ospedali Riuniti, Bergamo, Italy
A. Antinori, G. Antonucci
IMNI "L. Spallanzani" IRCCS, Rome, Italy
F. Castelnuovo
Spedali Civili, Brescia, Italy
N. Ladisa
Policlinico, Bari, Italy
M. Migliorino
Ospedale Civile, Busto Arsizio, Italy
S. Novati, C. Tinelli
IRCCS Policlinico S. Matteo, Pavia, Italy
A. De Luca
Università Cattolica S. Cuore, Rome, Italy
S. Lo Caputo
S.M. Annunziata, Firenze, Italy

Received: May 18, 2007 · Revision accepted: September 12, 2007
Published online: May 3, 2008

Patients and Methods

We conducted an analysis on patients prospectively enrolled in the observational MASTER database cohort. The distinguishing characteristic of this cohort is that it is based on the use of a common electronic database (Health & Notes version 3.5, Healthware s.p.a, Naples, Italy). The electronic database is implemented to manage daily activity of the outpatient HIV clinics. The resulting cohort is therefore an open cohort in which all patients followed in each center are continuously enrolled, without making any kind of selection (e.g., prospect of better adherence to keep the rate of patients lost to follow-up as low as possible).

Single databases were merged and data for all patients who started their first HAART from 1st January 1997 (first year of availability of protease inhibitors [PI] in Italy) to 31st December 2004 were extracted from the electronic database provided that HIV-RNA and CD4+ T cell count were recorded at baseline. Highly active antiretroviral therapy was defined as any antiretroviral regimen containing at least three drugs, including two nucleoside reverse transcriptase inhibitors (NRTI) plus one non-NRTI (NNRTI) or one PI either boosted or non-boosted with ritonavir.

A list of selected patients was then returned to each center in order to fill in available incomplete data, and recheck their quality. Collected data were as follows: demographics, clinical stage of HIV disease, risk factor for HIV acquisition, time of starting therapy, drugs included into the initial treatment, CD4+ T-cell counts and HIV plasma viral load at baseline, serological evidence of hepatitis C and/or B co-infection, CD4+ T-cell counts and HIV plasma viral load during the follow-up, modifications of the class of drugs added to the nucleoside backbone (i.e., from NNRTI to either single PI or boosted PI regimens, from single PI to either NNRTI or PI-boosted regimens, from PI-boosted to either NNRTI or single PI regimens).

Analysis was conducted on the observed data set, censoring the missing data at each follow-up time, irrespectively from change in the third class of drugs and therapeutic interruptions. The following two outcome measures were considered after 6, 12 and 18 months of therapy: (1) virological failure (i.e., viral load > 400 copies/ml), (2) immunological failure (i.e., lack of increase of CD4+ T-cell count by ≥ 45, 80 or 100/μl from baseline to month 6, 12 and 18, respectively [8, 9]). Moreover, changes of antiretroviral class added to the nucleoside backbone were also described at the same time points.

Treatment failure (either virological or immunological) occurring in at least one point of the follow-up was used as an outcome variable in logistic analysis aimed at exploring whether the trend overtime was independent of other factors which could also have had an impact. The study variables included age group, gender, race/ethnicity, type of antiretroviral regimens, CD4+ T-cell count, HIV-RNA, AIDS events occurring before HAART and calendar year at initiation of HAART. Odds ratios (OR) were calculated using the Intercooled STATA 8.0 for Windows 98/95 NT statistical software package (Stata Corporation, College Station, TX).

Results

General Characteristics of the Cohort

Overall, 3,648 previously naive patients started their first HAART regimen and were included in this study. Table 1 shows patient characteristics ranked by calendar year at initiation of HAART. Overall, patients were mostly males and Italians; however, percentages of non-European patients increased from 1997 to 2004 ($p < 0.001$). Non-European patients came mainly from sub-Saharan Africa (222/3,648 = 6%) and from central South America (103/3,648 = 3%). Heterosexual risk factor was reported in 36.9% of patients, increasing from 1997 to 2004 ($p < 0.001$). Intravenous drug use (IVDU) accounted for 34.2% of infections, while 14.9% of patients were declared to have acquired HIV infection through homosexual contacts. Risk factors for HIV acquisition were not declared in 10.7% of cases. Mean CD4+ T-cell count at baseline was 241 cells/μl and median HIV-RNA was 76,900 copies/ml. Anti-HCV antibodies were positive in 34.3% of patients, while HBsAg tested positive in 7% of subjects.

Prescriptions of Antiretroviral Drugs Over the Years

One thousand four hundred and forty-nine (39.7%) initial treatment combinations were based on 2 NRTIs + 1 NNRTI; 44.9% (1,633) on 2 NRTIs +1 PI; 15.2% (556) were based on 2 NRTIs + 1 boosted PI. Table 1 shows that prescriptions of NNRTI regimens increased from 1997 to 2004, as well as those of boosted-PI ($p < 0.001$). Also, the percentage of thymidine-sparing regimens (i.e., not including zidovudine or stavudine) increased from 1997 to 2004 ($p < 0.001$).

Virological, Immunological Failure and Change of Treatment Classes

Virological failure rates decreased over calendar years and at any follow-up time point (6, 12 and 18 months): at month 6, from 42.9% in 1997 to 8.1% in 2004 ($p < 0.001$); at month 12, from 42.1% in 1997 to 10.7% in 2004 ($p < 0.001$); at month 18, from 39.5% in 1997 to 8.2% in 2004 ($p < 0.001$) (Figure 1). The same trend, but less marked, was found for immunological failure: at month 6, from 29.3% in 1997 to 12.8% in 2004 ($p < 0.001$); at month 12, from 32.6% in 1997 to 20.7% in 2004 ($p < 0.001$); at month 18, from 29.8% in 1997 to 19.6% in 2004 ($p = 0.013$) (Figure 2). The percentages of patients who maintained the same initial type of HAART (i.e., class of the third drug added to the nucleoside backbone) and viro-immunological success after 18 months of HAART also rose significantly from 28.0% in 1997 to 35.5% in 2004 ($p = 0.004$). The rates of treatment success were not apparently influenced by mortality, which remained fairly stable over calendar years (less than 1% during the initial year of HAART).

Predictors of Treatment Failure

Logistic regression analysis confirmed a calendar year effect on the risk of virological failure independently of other variables, which also had an impact on treatment effectiveness as shown in table 2. On univariate logistic analysis, the risk of virological failure was lower in recent years in those who were older and started the first therapy

Table 1
Patient characteristics at baseline by calendar year at starting of HAART.

	Calendar year							
Characteristic	1997 *N* = 350	1998 *N* = 528	1999 *N* = 612	2000 *N* = 500	2001 *N* = 368	2002 *N* = 340	2003 *N* = 440	2004 *N* = 510
Qualitative variables (%):								
Male gender	73.4	74.2	71.1	72.8	73.1	70.3	72.1	71.9
HIV risk factor								
Homosexual	10.9	16.1	12.3	17.6	14.9	14.4	17.5	15.3
Heterosexual	28.6	29.4	36.9	38.6	44.6	42.9	41.4	35.7
IVDU	50.9	47.5	41.8	33	27.5	29.1	20.7	20.6
Not declared	5.1	3	4.2	6.2	7.1	7.6	12.9	17.9
Missing	0.6	0.9	0.8	1.4	1.5	1.5	1.4	3.5
Nationality								
Italian	93.7	88.1	84.6	78.4	77.9	79.1	74.8	74.9
Non-European	2.8	4.4	8.2	12	11.9	10.9	12	13.1
Other	2	1.1	1.1	2	1.9	3.2	3.2	8.6
Missing	0.9	6.6	6	7.6	8.1	6.7	10	8.6
HBsAg								
Positive	6	7	6.2	6.2	9.8	8.2	5.2	7.1
Negative	69.7	79.2	75.7	78.8	24.2	83.9	15.9	17.3
Missing	24.3	13.8	18.1	15	14.4	7.9	10.7	10.2
HCV-Ab								
Positive	42	45.6	38.4	30.6	31.8	32.7	27.1	26.5
Negative	35.7	39.8	43.1	53.8	52.7	57	61.3	62.5
Missing	22.2	14.6	18.5	18.5	15.5	10.3	11.6	11
Type of first HAART								
Single PI	99.4	87.9	58.8	38	20.7	22.1	12.7	8.6
NNRTI	0.3	9.8	36.6	54.4	61.9	47.3	57.5	58
Boosted PI	0.3	2.3	4.6	7.6	17.4	30.6	29.8	33.4
Thymidine backbone	99.7	99.1	93.8	97.4	94.6	90.6	59.8	51.7
Quantitative variables:								
Age (mean, SD)	35 (21–73)	36 (20–74)	37 (18–72)	37 (19–69)	39 (19–69)	39 (22–73)	40 (21–80)	39 (19–74)
CD4 + cell count [cells/mm^3] (median, IQR)	190.5 (70–379)	267 (101–302)	230 (96.5–385)	207 (81.5–344)	170 (58.5–293)	180 (77.5–277)	190 (90–290)	230.5 (89–307)
Viral load [Log_{10} copies/ml] (median, IQR)	5.0 (4.6–5.5)	4.8 (4.3–5.4)	4.8 (4.3–5.3)	4.8 (4.4–5.3)	4.9 (4.5–5.4)	4.9 (4.4–5.4)	4.9 (4.4–5.4)	4.9 (4.4–5.3)

IVDU: intravenous drug use; non-European: patients not coming from European Community; *HBsAg*: positive hepatitis B surface antigen; *HCV-Ab*: antibody to hepatitis C virus; *PI*: protease inhibitor; *NNRTI*: non nucleoside reverse-transcriptase inhibitor; PI: boosted: boosted protease inhibitor; *SD*: standard deviation; *IQR*: interquartile range

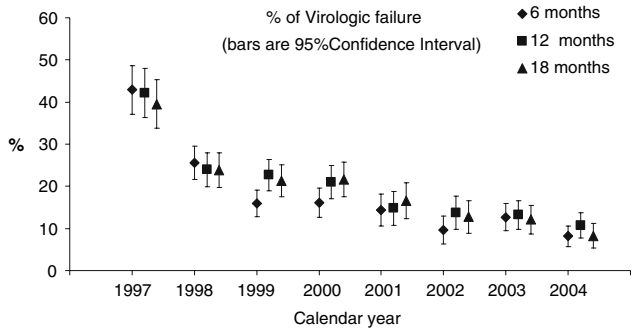

Figure 1. Virological failure at 6, 12 and 18 months by calendar year at starting of HAART.

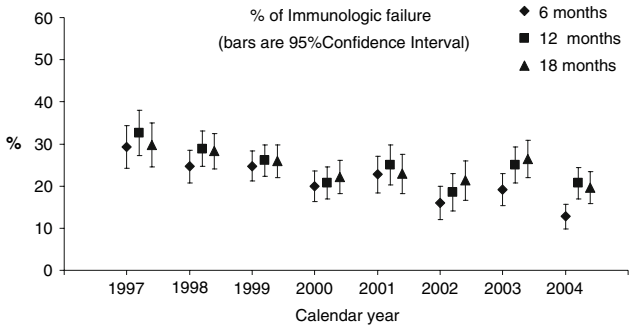

Figure 2. Immunological failure at 6, 12 and 18 months by calendar year at starting of HAART.

with NNRTI or boosted PI regimens. By contrast, a higher risk of virological failure was found in women patients with IVDU as a risk factor for HIV acquisition, positive HCV serology, higher CD4+ T-cell count at baseline and starting the first therapy with thymidine analogue drugs. Multivariate analysis revealed that starting therapy in the most recent years was a protective factor independent of the significant impact exerted by gender, IVDU, CD4+ T-cell count at baseline, NNRTI as the third drug and aging.

Table 3 shows the results of logistic analysis when a risk of immunological failure was studied. Again, the risk of failure was lower in the most recent years. Moreover, multivariate analysis showed that the risk of immunological failure was generally lower in patients with homosexual/bisexual risk and with higher HIV-RNA level at baseline; moreover, risk of immunological failure was higher in patients with higher CD4+ T cell count at baseline and who were seropositive for HCV-Ab.

Discussion

The data presented herein were generated from a cohort (MASTER) that is representative of public health services for HIV patients in Italy. In fact all patients had open access to medical care and free medications. Demographic characteristics of the study patients changed over time, reflecting the current epidemiology of HIV infection in Italy [10]. In particular, an increasing proportion of patients infected through heterosexual intercourse was found over the calendar years. Interestingly, a significant percentage of patients (10.7%) was declared to have acquired HIV by an unknown mode of transmission. This underlines the importance of preventative campaigns to reduce HIV risk. Moreover, a substantial proportion of patients came from developing countries, thus suggesting the need for a dedicated management to comply with language and cultural specificities of this population.

We found changes in the composition of the first HAART regimens occurring over the study years. In fact, NNRTI-based regimens were increasingly prescribed, as well as regimens including boosted-PI and non-thymidine analogue backbones. The change of drug classes and drugs over time was a result of their efficacy in RCT. However, the efficacy of an antiretroviral regimen in RCT is demonstrated in ideal circumstances (i.e., ''ideal'' patients and ''ideal'' expert clinicians). Therefore, it is important to verify the actual effectiveness of the antiretroviral regimens in the real clinical practice.

With this objective in mind, we found that the evolution of drug prescription correlated with improved effectiveness of HAART. Strikingly, percentages of undetectable viral loads became similar to those reported by RCT. A similar trend was recently found in a multicenter cohort of 3,825 patients from countries not including Italy, who started treatment up to the year 2002 and composed of lower percentage of patients acquiring HIV infection through IVDU than in our study [11]. Also, a positive trend of immunological success was evident from our study, although not consistently found in each calendar year.

The improvement in short-term effectiveness of HAART was probably due to the intrinsic characteristics of the new regimens in terms of potency, but also simplicity of use, better tolerability and toxicity profiles and consequently better patient adherence. For instance, the positive impact of NNRTI regimens was demonstrated through multivariable analysis, indicating a 23% reduction in the risk of virological failure. Moreover, an increased viro-immunological success, without changing the class of drugs added to the nucleoside backbone, was found. However, we also found an independent effect of the calendar year by itself, with a 74% reduction in the risk of virological failure in the year 2004 with respect to 1997. Also, this effect was independent of other possible confounders evolving over the calendar years or associated with the outcome such as gender, patient age, ethnicity, risk factor for HIV acquisition, baseline HIV plasma viral load, baseline CD4+ T-cell count and status of hepatitis co-infections. Therefore, the association with the calendar year may reflect other factors not captured in the present analysis, such as specific type of drugs but also better experience

of the treating clinicians and improvement of the overall healthcare system.

Our study has both strengths and limitations. One important strength is that the MASTER cohort is representative of public services for HIV patients and reflects the general patient population in Italy. Moreover, we applied multivariate statistical models. Factors associated with the clinical outcome should promote further studies and possibly target interventions to improve patient care. Our study also has limitations. First, our analysis was limited by lack of adherence information. Second, data on important psycho-social factors (including cultural background or mental illnesses) were not recorded and appropriate evaluation of the quality of care was not performed. Third, we did not study the effects of evolving HAART on patient survival. However, viro-immunolog-

Table 2
Factors associated with virological failure.

Variable	Crude		Adjusted	
	OR (95% CI)	p	OR (95% CI)	p
First therapy started in year 1998 (vs 1997)	0.53 (0.41–0.70)	< 0.001	0.56 (0.42–0.74)	< 0.001
First therapy started in year 1999 (vs 1997)	0.38 (0.29–0.49)	< 0.001	0.44 (0.33–0.59)	< 0.001
First therapy started in year 2000 (vs 1997)	0.37 (0.28–0.49)	< 0.001	0.49 (0.36–0.67)	< 0.001
First therapy started in year 2001 (vs 1997)	0.32 (0.23–0.43)	< 0.001	0.48 (0.33–0.68)	< 0.001
First therapy started in year 2002 (vs 1997)	0.23 (0.16–0.32)	< 0.001	0.34 (0.23–0.49)	< 0.001
First therapy started in year 2003 (vs 1997)	0.20 (0.15–0.28)	< 0.001	0.36 (0.24–0.52)	< 0.001
First therapy started in year 2004 (vs 1997)	0.15 (0.11–0.21)	< 0.001	0.26 (0.18–0.39)	< 0.001
Female gender (vs male)	1.17 (1.00–1.37)	0.049	1.22 (1.02–1.47)	0.030
Older age (per year older)	0.96 (0.95–0.97)	< 0.001	0.97 (0.96–0.98)	< 0.001
IVDU risk factor (vs others)	1.83 (1.55–2.17)	< 0.001	1.35 (1.06–1.71)	0.012
Baseline CD4+ (per 100/mm^3 higher)	1.11 (1.07–1.14)	< 0.001	1.06 (1.02–1.10)	0.001
HCV-Ab positive versus others	1.67 (1.43–1.96)	< 0.001	Not significant	
Boosted PI in first HAART (vs PI)	0.44 (0.35–0.55)	< 0.001	Not significant	
NNRTI in first HAART (vs PI)	0.49 (0.42–0.57)	< 0.001	0.77 (0.63–0.95)	0.016
Thymidine analogue backbone (vs no thymidine analogue)	2.33 (1.83–2.97)	< 0.001	Not significant	

Only variables associated with outcome with a p-value < 0.2, so that they were input in the multivariable model, are shown here.
IVDU: intravenous drug use; extra E.C.: patients coming from outside Italy and European Community; *HCV-Ab*: antibody to hepatitis C virus; *PI*: protease inhibitor; *NNRTI*: non nucleoside reverse-transcriptase inhibitor; PI boosted: boosted protease inhibitor; *OR*: odds ratio; 95% CI: 95% confidence interval

Table 3
Factors associated with immunological failure.

Variable	Crude		Adjusted	
	OR (95% CI)	p	OR (95% CI)	p
First therapy started in year 1999 (vs 1997)	0.73 (0.56–0.96)	0.023	0.71 (0.54–0.95)	0.021
First therapy started in year 2000 (vs 1997)	0.62 (0.47–0.82)	0.001	0.70 (0.51–0.96)	0.025
First therapy started in year 2001 (vs 1997)	0.67 (0.50–0.91)	0.009	Not significant	
First therapy started in year 2002 (vs 1997)	0.49 (0.36–0.67)	< 0.001	0.57 (0.39–0.81)	0.002
First therapy started in year 2003 (vs 1997)	0.72 (0.54–0.95)	0.022	Not significant	
First therapy started in year 2004 (vs 1997)	0.46 (0.34–0.61)	< 0.001	0.53 (0.37–0.77)	0.001
IVDU risk factor (vs others)	1.64 (1.41–1.93)	< 0.001	Not significant	
Homo/bisexual risk factor (vs others)	0.80 (0.64–0.99)	0.042	0.76 (0.61–0.95)	0.018
Baseline CD4+ (per 100/mm^3 higher)	1.15 (1.11–1.19)	< 0.001	1.11 (1.07–1.15)	< 0.001
Viral load (Log_{10} copies/ml)	0.69 (0.64–0.76)	< 0.001	0.72 (0.66–0.79)	< 0.001
HCV-Ab positive versus others	1.90 (0.64–2.21)	< 0.001	1.58 (1.28–1.95)	< 0.001
Boosted PI in first HAART (vs PI)	0.81 (0.67–0.99)	0.045	Not significant	
NNRTI in first HAART (vs PI)	0.77 (0.67–0.89)	0.001	Not significant	
Thymidine analogue backbone (vs no thymidine analogue)	1.23 (1.01–1.50)	0.033	Not significant	

Only variables associated with outcome with a p-value < 0.2, so that they were input in the multivariable model, are shown here.
IVDU: intravenous drug use; extra E.C.: patients coming from outside Italy and European Community; *HCV-Ab*: antibody to hepatitis C virus; *PI:* protease inhibitor; *NNRTI*: non nucleoside reverse-transcriptase inhibitor; PI boosted: boosted protease inhibitor; *OR*: odds ratio; 95% CI: 95% confidence interval

ical improvement is likely to be correlated with clinical benefits, at least considering HIV-related opportunistic infections and deaths. Indeed, several studies have yet demonstrated sustained drops in mortality and morbidity after the introduction of HAART [2–4].

In conclusion, it appeared that in the general Italian population of HIV-positive patients under care, the evolution of antiretroviral treatment corresponded to improved effectiveness of HAART. In the most recent years, short-term viro-immunological benefits approximated RCT results.

Acknowledgments

Financial Support: Supported by Programma Nazionale AIDS, Istituto Superiore di Sanità (30G.5).

The composition of the MASTER Cohort is as follows (cities where clinical centers are based are in brackets): G. Carosi, C. Torti, M. Puoti and E. Quiros-Roldan (Brescia); A. Antinori, F. Antonucci (INMI L. Spallanzani, Rome); R. Cauda, A. De Luca (Università Cattolica del Sacro Cuore, Rome); G. Angarano, A. Saracino (Foggia); A. D'Arminio, P. Cicconi (Milan); F. Mazzotta, S. Lo Caputo, N. Marino (Florence); L. Minoli, R. Maserati, C. Tinelli (Pavia); F. Ghinelli, L. Sighinolfi (Ferrara); G. Pastore, N. Ladisa, (Bari); T. Quirino, M. Migliorino (Busto Arsizio); F. Suter, F. Maggiolo (Bergamo).

References

1. Palella FJ, Delaney KM, Moorman AC, loveless MO, Fuher J, Satten GA, Aschman DJ, Holmberg SD: Declining morbidity and mortality among patients with advanced immunodeficiency virus infection. N Engl J Med 1998; 338: 853–860.
2. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, Knysz B, Dietrich M, Phillips AN, Lundgren JD, EuroSIDA Study Group Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 2003; 362: 22–29.
3. Sterne JAC, Hernan MA, Ledergerber BA, Tilling K, Weber R, Sendi P, Rickenbach M, Robin JM, Egger M, The Swiss Cohort Study: Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005; 366: 378–384.
4. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT, Vaet M, Obel N: Survival of persons with and without HIV infection in Denmark, 1995–2005. Ann Int Med 2007; 146: 87–95.
5. Gulick RM, Ribaudo HJ, Shikuma CM, Lustgarten S, Squires KE, Meyer WA, Acosta EP, Schackman BR, Pilcher CD, Murphy RL, Maher WE, Witt MD, Reichman RC, Snyder S, Klingman KL, Kuritzkes DR: AIDS Clinical Trials Group Study A5095 Team Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med 2004; 350: 1850–1861.
6. Shafer RW, Smeaton LM, Robbins GK, De Gruttola V, Snyder SW, D'Aquila RT, Johnson VA, Morse GD, Nokta MA, Martinez AI, Gripshover BM, Kaul P, Haubrich R, Swingle M, McCarty SD, Vella S, Hirsch MS, Merigan TC, AIDS Clinical Trials Group 384 Team: Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 2003; 349: 2304–2315.
7. Bartlett JA, Fath MJ, DeMasi R, Hermes A, Quinn J, Mondou E, Rosseau F: An updated systematic overview of triple combination therapy in antiretroviral-naive HIV-infected adults. AIDS 2006; 20: 2051–2064.
8. Renaud M, Katlama C, Mallet A, Calvez V, Carcelain G, Tubiana R, Jouan M, Caumes E, Agut H, Bricaire F, Debre P, Autran B: Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. AIDS 1999; 13: 669–676.
9. Le Moig V, Thiebaut R, Chene G, Leport C, Cailleton V, Michelet C, Fleury H, Herson S, Raffi F, APROCO Study Group: Predictors of long-term increase in CD4 (+) cell counts in human immunodeficiency virus-infected patients receiving a protease inhibitor-containing antiretroviral regimen. J Infect Dis 2002; 185: 471–480.
10. Suligoi B, Boros S, Camoni L, Lepore D, Ferri M, Roazzi P: Aggiornamento dei casi di AIDS notificati in Italia e delle nuove diagnosi di infezioni da HIV al 31 dicembre 2005. Not Ist Super Sanità 2006; 19: 3–23.
11. Lampe CF, Gatell JM, Stazewski S, Johnson MA, Pradier C, Gill MJ, De Lazzari E, Dauer B, Youle M, Fontas E, Krentz HB, Phillips AN: Changes over time in risk of initial virological failure of combination antiretroviral therapy. Arch Int Med 2006; 166: 521–528.