Peer reviewed article

Morbidity and mortality in HIV-infected individuals – a shift towards comorbidities

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Summary

Combination antiretroviral therapy (cART) has dramatically improved the prognosis of HIV-infected persons to a level close to a normal life expectancy in a significant proportion of treated individuals. On starting cART HIV-induced immune deficiency can be prevented or, if already present, reconstituted. Remaining morbidity and mortality is partly due to late presentation of patients, when CD4-T-cells have already fallen below 200 cells/μL often accompanied by symptomatic disease. However, at present morbidity and mortality are mainly related to comorbidities such as hepatitis and tumours at least partly associated with HIV infection. It should be noted that, as HIV-infected patients become older, long-term toxicity of antiretroviral drugs may play an important role in increasing the risk of cardiovascular diseases. The changing pattern of HIV-associated diseases may indicate the need for specific preventive measures in this population.

Key words: HIV/AIDS; co-morbidities; morbidity; mortality

Introduction

HIV/AIDS remains a major public health issue in Europe, where an estimated 2.4 million individuals are currently living with HIV/AIDS, a large proportion in Eastern Europe [1]. With the introduction of cART and the advent of protease inhibitors in 1994–1996 the hope of curing HIV was the over-optimistic vision with the dogma "hit hard – hit early" (table 1). Although HIV viraemia could be durably reduced to levels below the limit of detection, HIV cannot be eradicated with currently available antiretroviral drugs and lifelong treatment is required. Hence the key goal of cART is to achieve sustained virological suppression in order to restore and preserve immunological function, prevent opportunistic diseases and reduce mortality. The long-term virological and immunological efficacy of cART was documented in many longitudinal studies [2–11]. Due to the high frequency of long-term toxicity, particularly of first generation antiretrovirals, in earlier years the threshold for starting cART was defined at a CD4-T-cell count of 200 cells/μL. This is the threshold where the risk of AIDS-defining diseases starts to increase sharply. Recent large observational studies, however, support the use of cART in all individuals with a CD4 cell count <350 cells/μL, since the incidence rate of both AIDS and non-AIDS-defining conditions, including cardiovascular diseases, liver-related events, renal diseases and certain malignancies, was shown to increase progressively as the CD4 cell count decreases from 350 to 200

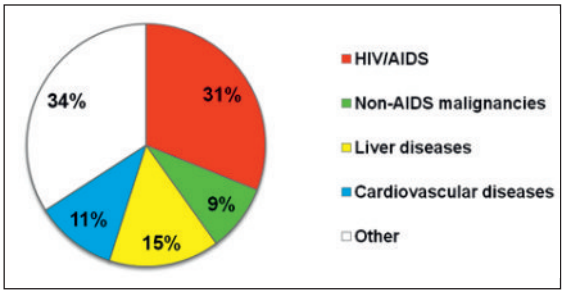
Table 1

Therapeutic concepts and threshold when to start cART have changed over time, in view of lower long-term toxicity of antiretrovirals and improved survival of treated individuals. Compiled from Benson et al. at http://aidsinfo.nih.gov/guidelines/2008

Years	Goals	Issues
1996	Hit hard, hit early	Hope of Cure
	CD4	
1997	<500	Conservation of immunity
2000	<350	ART works at lower levels
2003	<200	ART long-term toxicity
2007	<350	Reduce morbidity, less toxicity
2008	<350 or higher	Comorbidity (non-AIDS), readiness
2009	>350	Recent observational studies indicate a risk reduction when cART is initiated earlier [13, 14]

Figure 1

Causes of death among HIV-infected individuals in Europe [12].



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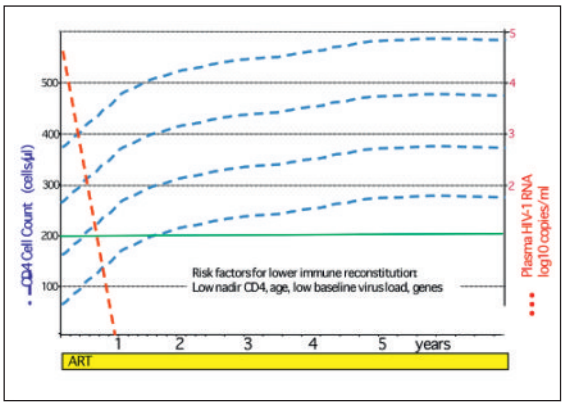


Figure 2

cART has dramatically improved the prognosis of HIV-infected individuals, and even in patients starting cART late with low CD4-T-cell count immune recovery is very likely to build up often to normal CD4-T-cell levels or at least over the critical threshold of 200 CD4-T-cells/µL. The curves are idealised summations of data from multiple studies [22, 23, 25]. Patients with initially low levels, however, may show recovery to lower absolute CD4-T-cell levels. Hence patients starting cART with different baseline CD4-T-cell counts/µL may not show convergence of immune recovery on normal levels.

cells/µL. Along with these concepts, recommended thresholds for the start of cART were changed in the guidelines (tab. 1). A recent study (fig. 1) shows that two thirds of deaths are no longer directly related to AIDS-defining diseases [12]. Two recent observational studies indicate that even higher thresholds for starting cART i.e., >350 CD4 cells/µL, were associated with a reduction in mortality risk [13, 14].

Table 2 illustrates the increase in potency and impact of cART on mortality since 1996. Major European cohort studies such as EUROSIDA [7] , the Swiss HIV Cohort Study [11] and the Danish Cohort Study [6] reported a life prolongation between 10 and 35 years, chiefly depending on adherence to cART and comorbidities such as intravenous drug use and/or chronic hepatitis C. Recently, the large international observational study ART-CC reported a prolongation of life expectancy of another 43 years for individuals starting cART at age 20 years [15].

Combination antiretroviral therapy

cART should be started before the risk of opportunistic diseases increases, i.e. at the threshold of 350 CD4-T-cells/µL. According to most guidelines a triple combination therapy of two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor is the preferred initial regimen [16–19]. Several antiretroviral drugs from six drug classes are currently available with somewhat different efficacy, pill burden, and potential side effects (table 3). The presence of transmitted HIV drug resistance, comorbidities, interactions with other required medications, psychiatric disorders including active drug use, and socioeconomic barriers should be carefully considered before starting cART.

With these therapies the virological and immunological outcome is excellent. For example, in a recent study of the Swiss HIV Cohort Study the overall first-year response was between 87.1 and 96.9%, depending on whether or not treatment had to be changed [20].

Comorbidities and mortality

Immune reconstitution

With cART, we within the Swiss HIV Cohort Study and others demonstrated that absolute numbers of CD4-T-cells continue to rise to usually normal ranges for the majority of HIV-infected individuals (fig. 2) [21–27]. Hence, even in patients starting cART late with a low CD4-T-cell count, in many cases immune recovery is very likely to build up to normal CD4-T-cell levels or at least over the critical threshold of 200 CD4-T-cells/µL. Importantly, the reconstitution of CD4-T-cells has dramatically reduced the risk of all

Table 2

Combination antiretroviral therapy has dramatically decreased the mortality of HIV-infected individuals.

Year	Study		Design	≈ Decrease mortality %
1996	Delta [59]	RCT	AZT vs dual cART	30–50
1996	ACTG 175 [4]	RCT	AZT vs dual cART	
1997	ACTG 320 [5]	RCT	Dual vs cART	70–80
1997	SHCS [2]	OS	No cART vs cART	
1998	HOPS [9]	OS	No cART vs cART	
2003	EuroSIDA [7]	OS	cART: 1996/97 vs 1998/2002	Continuous decrease of mortality
2005	SHCS [11]	OS	No cART vs cART	86
2007	Danish Cohort [6]	OS	HIV versus non-HIV	≈ 10–38 years of life prolongation after start of cART
				≈ Normal life expectancy (?)
2008	ART-CC [15]	OS	cART: 1996/99 vs 2003/05	Life expectancy for another 43 years if cART started at age of 20 years

ACTG = Aids Clinical Trial Group, SHCS = Swiss HIV Cohort Study, HOPS = The HIV Outpatient Study, ART-CC = Antiretroviral Therapy – Cohort Collaboration, AZT = Zidovudin, cART = combination antiretroviral therapy, RCT = Randomised Clinical Trial, OS = Prospective Observational Study

Table 3

Currently approved drugs for antiretroviral therapy according to drug class.

Nucleoside reverse transcriptase inhibitors (NRTIs)
Zidovudine (Retrovir®, ZDV, AZT)
Didanosine (Videx®, ddI)
Zalcitabine (Hivid®, ddC)
Stavudine (Zerit®, d4T)
Lamivudine (Epivir®, 3TC)
Zidovudine/lamivudine (Combivir®)
Abacavir (Ziagen®, ABC)
ZDV/3TC/ABC (Trizivir®)
Emtricitabine (Emtriva®, FTC)
ABC/3TC (Kivexa®)
Tenofovir (Viread®, TDF)
TDF/FTC (Truvada®)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
Nevirapine (Viramune®, NVP)
Delavirdine (Rescriptor®, DLV)
Efavirenz (Stocrin®, EFV)
Etravirine (Intelence®, ETV)

Protease inhibitors (PIs)
Saquinavir (Invirase®, SQV)
Ritonavir (Norvir®, RTV)
Indinavir (Crixivan®, IDV)
Nelfinavir (Viracept®, NFV)
Lopinavir/r (Kaletra®, LPV/r)
Fos-amprenavir (Lexiva®, Telzir®, fAPV)
Atazanavir (Reyataz®, ATV)
Tipranavir (Aptivus®, TPV)
Darunavir (Prezista®, TMC114)
Fusion inhibitor
Enfuvirtide (Fuzeon®, T-20)
Entry inhibitor
Maraviroc (Celsentri®)
Integrase inhibitor
Raltegravir (Isentress®)

opportunistic infections and the overwhelming majority of HIV-associated tumours. Risk factors for lower CD4-T-cell immune reconstitution are a low nadir CD4-T-cell count, more advanced age, certain HLA genes and a low viral load at baseline [22, 23]. However, the incidence of opportunistic diseases has fallen dramatically even in individuals with a lower increase in CD4-T-cells, provided the viral load is suppressed with cART. Hence, as shown by the outcome with cART, CD4 functionality is reconstituted to a high degree. However, earlier and recent studies indicate that specific comorbidities exist which are caused either by a specific lack of immunity such as that shown for CNS non-Hodgkin lymphoma [28], viral co-infections such as polyoma virus [29], or HIV-induced immune activation increasing adverse effects of antiretroviral drugs such as cardiovascular diseases.

As shown in table 4, different large-scale observational studies and randomised clinical trials indicate that a lower current CD4-T-cell count is significantly associated with higher risk of non-AIDS malignancies, liver diseases, cardiovascular diseases and renal diseases [30].

Table 4

Association between current CD4-T-cell count and non-AIDS complications [30].

Study	**Is a lower current CD4-T-cell count significantly associated with increased risk?**			
	Non-AIDS malignancies	**Liver disease/death**	**Cardiovascular diseases/death**	**Renal disease/death**
FIRST	Yes	No	Trend, NS	Yes
D:A:D	Yes	Yes	Trend, NS	Yes
CASCADE	Yes	Yes	Yes	NA
SMART	Trend, NS	Yes	Trend, NS	Trend, NS

CASCADE = Concerted Action on Seroconversion to AIDS and Death in Europe; D:A:D = Data Collection on Adverse Events of Anti-HIV Drugs; FIRST = Flexible Initial Retrovirus Suppressive Therapies; SMART = Strategies for Management of Antiretroviral Therapy; NS = Not statistically significant

Non-AIDS malignancies

Although the incidence of AIDS-defining tumours such as Kaposi's sarcoma and cerebral lymphoma has sharply declined with the advent of cART, a lower impact has been observed on the incidence of non-Hodgkin's lymphoma and cervical cancer. Further, large-scale observational studies have recently reported a 2- to 3-fold higher risk of developing selected non-AIDS malignancies in HIV-infected patients than in the general population [31–34]. These malignancies, which appear to have an earlier onset and a worse prognosis in HIV-infected individuals, include Hodgkin's disease, lung, head and neck cancers, liver and anal cancers. The increase in non-AIDS-defining malignancies is partly explained by the improvement in life expectancy due to cART, along with an only partial immune recovery allowing a larger number of cancers with long latent periods to manifest clinically. Furthermore, the 3-fold excess risk of cancers of the trachea, bronchus and lung in HIV-infected individuals seems to be directly attributable to the high smoking prevalence in this population, particularly intravenous drug users [32, 35]. Interestingly, in co-infected patients with hepatitis B and C, the occurrence of hepatocellular carcinoma was increased with severe immunosuppression, regardless of cART use [36].

In conclusion, the increased incidence of selected non-AIDS malignancies and the residual increased risk of non-Hodgkin's lymphoma indicates that specific immunity to certain tumours may be lacking, allowing such tumours to occur. In this context it is paramount that prevention, screening and specific interventions such as smoking cessation programmes are implemented in the routine care of HIV-infected individuals [35].

Liver diseases

Liver disease from chronic hepatitis B and C infection was recognised as the most important cause of non-AIDS-related death in a large cohort of HIV-infected individuals in Europe, particularly in intravenous drug users, accounting for 14.5% of all causes of death [12]. Although severe immunodeficiency was associated with increased mortality in individuals co-infected with HIV and hepatitis C, the rate of progression of liver fibrosis did not significantly change after the introduction of cART, suggesting that other pathophysiological mechanisms may be involved in the progression of hepatitis C in this population [37, 38]. Efforts should be made to establish effective treatment for HIV/hepatitis C co-infected individuals. However, this may be difficult, as is shown by a study investigating eligibility for HCV treatment [39]. This study demonstrated that despite clinical and psychosocial obstacles encountered in clinical practice, HCV treatment in HIV-co-infected individuals is feasible. However, this study also demonstrated that more than 50% of the HCV-treated patients would have been excluded from larger randomised clinical trials due to demographic, clinical and laboratory criteria.

Lipid disorders and cardiovascular diseases

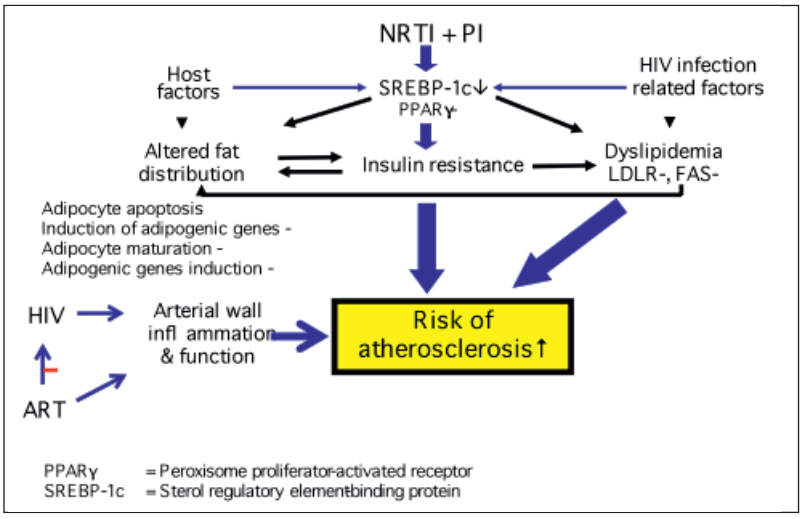
cART is generally well tolerated and newer antiretrovirals are associated with fewer side effects. However, treatment changes due to adverse events such as gastrointestinal intolerance, central nervous system symptoms, hepatotoxicity and lipid disturbances are still frequent. A study of the Swiss HIV Cohort Study indicates that a switch of cART in patients starting therapy between 2000 and 2005 occurred in approximately 50% within the first year of treatment [20].

Metabolic complications including dyslipidaemia, body fat abnormalities and insulin resistance may lead to an increased risk of cardiovascular disease. The pathogenesis of lipid disturbances is multifactorial, involving effects of antiretroviral treatment, HIV itself, and genetic and other host factors (fig. 3) [40–43]. Nucleoside reverse transcriptase inhibitors and protease inhibitors influence different factors regulating lipid metabolism. Mediated by sterol regulatory element binding protein-1c (SREBP1) and peroxisome proliferator-activated receptor (PPAR), insulin resistance is increased, fat distribution is altered and dyslipidaemia occurs [44]. HIV infection itself also induces arterial wall inflammation [45–48]. cART influences atherosclerosis twofold. On the one hand, cART decreases and impairs HIV replication, thereby decreasing macrophage activation as well as endothelial activation and hence protecting against atherosclerosis. On the other hand, cART elevates density LDL cholesterol and triglycerides contributing to inflammatory processes, monocyte activation and thereby atherosclerosis [40, 41, 45–48].

There are ample identified cardiovascular risk factors, such as cigarette smoking, hypertension, diabetes, abdominal obesity, family history and others. HIV itself and specific antiretroviral drugs increase the cardiovascular risk. The D:A:D study (Data Collection on Adverse Events of Anti-HIV Drugs), a large prospective observational study compiling data of more than 20 000 patients, indicated that the relative incidence of myocardial infarction risk per year of cART was 1.16. The D:A:D study showed that protease inhibitors were associated with this increased risk. Recently, the D:A:D study group associated the use of abacavir and didanosine, two nucleoside reverse transcriptase inhibitors, with an increased relative risk of myocardial infarction of 1.9 and 1.5, respectively [49–51]. This association remained significant after adjustment for HIV-RNA levels, CD4-T-cell count, dislipidaemia, blood pressure, diabetes, fat loss and gain, or latest glucose. However, these results could not be confirmed in a smaller database compiling data of 54 clinical trials where the incidence of myocardial infarction was similar regardless of therapy i.e., whether abacavir was given or not [52]. An analysis of a subset of patients randomised to the continuous cART arm of SMART (Strategies for Management of Antiretroviral Therapy) demonstrated again that abacavir was associated with an increased risk of my-

Figure 3

The pathogenesis of lipid disorders is multifactorial, involving effects of antiretroviral treatment, HIV itself and genetic and other host factors.



Courtesy Peter Reiss, MD, Amsterdam, The Netherlands

ocardial infarction including elevated biomarkers such as sensitivity-C-reactive protein and high interleukin-6 [53]. However, the authors stated that patients a priori at an excess and underlying risk of cardiovascular disease may have been preferentially placed on abacavir [53].

It is very difficult to judge what is the net effect of HIV-infection together with cART for the development of atherosclerosis. Two recent studies are noteworthy in this context. Kaplan RC et al. measured subclinical carotid artery lesions and common carotid artery intima thickness in participants in the Women's Interagency HIV Study and Multicenter AIDS Cohort Study [54]. In this study, no consistent association of antiretroviral medications with carotid atherosclerosis was observed, except for a borderline significant association between protease inhibitor use and carotid lesions in men. However, they found that beyond traditional cardiovascular disease risk factors, low CD4-T-cell count was the most robust risk factor for increased subclinical carotid atherosclerosis in HIV-infected individuals. Hence, HIV-disease stage critically influenced cardiovascular risk. Secondly, Kingsley LA et al. showed in a cross-sectional study of 947 male participants of the Multicenter AIDS Cohort Study (MACS) [55], that the prevalence of coronary artery calcification was marginally increased only among long-term cART users.

Kidney diseases

HIV-associated nephropathy, related to direct effects of HIV, may be prevented and treated with antiretrovirals. However, with increasing longevity of treated HIV-infected individuals, kidney diseases have emerged as a significant cause of morbidity and mortality in this population. In addition to the increasing prevalence of diabetes mellitus and hypertension, partly derived from metabolic complications of cART, HIV-infected individuals are at higher risk of kidney diseases as a consequence of hepatitis C co-infection and injection drug use. Moreover, some antiretroviral drugs such as indinavir, ritonavir and, more recently, tenofovir, have been associated with nephrotoxicity [56–58], highlighting the need for close monitoring of renal function in treated HIV-infected individuals.

Conclusions

cART has drastically reduced HIV-associated morbidity and mortality. However, cART is associated with long-term toxicity which includes primarily metabolic disturbances and cardiovascular diseases. Other comorbidities, i.e. chronic hepatitis and tumours, are becoming more important in an ageing HIV population. With close to normal life expectancy and significantly prolonged duration of cART, HIV-infected individuals are becoming older and increasingly likely to experience a broad range of comorbidities with increased mortality. In this context ongoing and future studies will investigate the long-term effects of cART on prevention and treatment of HIV-associated brain injury, specifically milder forms of cognitive impairment. This includes studies on the impact of poor CNS penetration of most antiretrovirals. Knowledge of specific comorbidities and long-term toxicities is essential if such complications are to be prevented or detected early enough.

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