Highly active antiretroviral therapy (HAART) has changed the face of HIV infection and AIDS into a treatable, chronic illness in resource-rich areas of the world. The hope is that we will overcome availability and distribution issues in resource-poor settings so the same is true in these regions of the world in the future. When available, HAART has dramatically decreased the incidence of opportunistic infections, which were frequently the direct cause of mortality during HIV infection. The paradox of this situation is that morbidities that were never relevant previously, because of truncated longevity before HAART, have now come to the fore as important aspects of HIV-related management. Diseases that shorten life in patients without HIV infection must now be attended to with particular rigor in caring for patients with HIV infection. This is especially true since the manifestations of these co-morbidities are often worsened by HIV infection, and special considerations, including drug interactions, must be taken into account.

Cardiovascular diseases are especially important in this regard because of their prevalence in the population and their frequent relationship to morbidity and mortality. Whether the heart and vascular system are affected by HIV infection is in little doubt, although the extent of these effects in different populations, and the relative contribution of HIV infection compared to classical risk factors, is a matter of some controversy. Much data has accumulated to suggest that there are significant effects of HIV, and concomitant therapy, on the cardiovascular system.

The chapters in this book describe what is clearly understood, and what is not. They go on to present the data upon which these opinions are based, and to make practical suggestions for proper diagnosis and management. They make important reading for researchers and clinicians in this field, both to provide the clinical basis for basic research that will inform new diagnostic and treatment paradigms, and to suggest the best, current therapies for these maladies.

Perhaps the most urgent area for research, leading to a more concise, mechanism-based understanding of pathogenesis, is
HIV-associated lipodystrophy. This catch-all phrase actually subsumes several areas that may have distinct pathophysiologic etiologies. Lipoatrophy has in some ways become the new “scarlet letter” of HIV infection, a distinction previously held by cutaneous Kaposi’s sarcoma. The cause of this manifestation, characterized by thinning of the face, arms, legs, and buttocks, remains unclear, as does the relative contribution of HAART and HIV infection to these changes. Fat redistribution syndrome, characterized by fatty deposits of the neck and abdomen (“buffalo hump” and “protease paunch”) most often occurs during HAART, but whether fat redistribution is associated with an increased risk of cardiovascular disease, and whether lipoatrophy engenders similar risk, remains uncertain.

HAART may lead to changes in serum lipids, and it is likely that these changes increase the risk of atherosclerotic heart disease, myocardial infarction, and stroke. Whether or not these lipid changes during HIV infection carry the same, or greater, risk compared to the general population without HIV infection, it is clear that clinicians should measure these changes and treat them accordingly. In this context, it is often necessary to know the relative magnitude of lipid changes with various antiretroviral agents so that treatment regimens can be modified appropriately if standard lipid-lowering therapy does not suffice. It is also crucial for clinicians to know the many drug–drug interactions that can occur and that modify the efficacy and tolerability of antiretroviral drugs and lipid-lowering agents. Newer diagnostic modalities, that have both clinical and research applications, are currently being assessed, as are the best drugs to use in these situations.

Other metabolic changes that occur during HIV infection, or are modified by HIV infection, also affect cardiovascular risk and optimal treatment of these disorders. Diabetes mellitus, associated with insulin resistance and the metabolic syndromes mentioned above, may have exaggerated effects on the cardiovascular system during HIV infection. Antiretroviral drugs may also be associated with lactic acidosis and acute, life-threatening illness, or may cause life-threatening pancreatitis through drug-induced hypertriglyceridemia or direct toxicity.

Other HIV-related effects may occur directly on the myocardium or pulmonary tissues, and lead to cardiomyopathy or HIV-associated pulmonary arterial hypertension. As longevity increases for those with HIV infection, a fuller understanding of these disorders becomes important for proper diagnosis and treatment. It is likely that the immune activation that occurs during HIV infection, even with effective HAART, is related to the expression of these diseases during HIV infec-
tion. Once again, it is difficult to determine the relative contribution of HIV infection and risk factors such as amphetamine, tobacco, or cocaine use, but it is clear that HIV infection alone can lead to cardiomyopathy and HIV-associated pulmonary hypertension. There is an important need to understand the natural history of these disorders to better plan when certain diagnostic and therapeutic interventions should be initiated.

This book should be read by all those interested in the cardiovascular complications that occur during HIV infection. The gold mine of information contained herein will stimulate new ideas about pathogenesis, inform in vitro and animal model research to test these hypotheses, and lead to patient-oriented research and clinical trials to test practical interventions that might improve diagnosis and treatment of cardiovascular co-morbidities. In this context, the combined knowledge and expertise of scientists and clinicians in the fields of infectious diseases, lipid metabolism, endocrinology, cardiology, and other relevant subspecialties must be brought to bear to unravel the mysteries that still exist, so that we may optimally prevent illness and care for those who suffer from the sometimes devastating effects of cardiovascular disease.

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Never in the history of humanity has knowledge progressed as quickly as in the field of AIDS. Over a period of 15 years, successive discoveries of the disease, its viral origin, the virus responsible, its physiopathology and highly effective therapies have led to spectacular improvement in life expectancy and in the quality of life of people who have access to these treatments.

However, this progress in therapy has been accompanied by initially unforeseeable anomalies, such as abnormalities in lipid and glucose metabolism and modifications in fat distribution, particularly in perivisceral and trunkal accumulation as well as pseudo-obesity usually accompanied by peripheral atrophy.

Several of these anomalies constitute risk factors for cardiovascular diseases and may be predictors of these diseases. Over time, most investigators have come to accept that HIV-infected patients are at an increased risk for cardiovascular complications.

However, several issues remain unclear:
• Does the increased risk merely reflect modification of the usual factors: metabolic disorders, tobacco consumption, infectious context related to HIV infection or opportunistic infections, inappropriate immune and cytokine response, or genetic background?
• The physiopathology of disorders in glucose or lipid metabolism remains to be clarified. It is unclear whether they result from treatment, use of a specific medication, use of a therapeutic class of medication, or an association of treatments. Here, too, genetic background may well be a factor, along with the history of the individual’s HIV infection.

It is particularly difficult to devise a therapeutic strategy under these conditions, especially since the efficacy of the usual lipid- or glucose-modifying medication is not established, and the benefit of any eventual correction of such biological anomalies in this population is unclear. The issue is further complicated by the many drug interactions between antiretroviral medications and medications likely to act on the lipid metabolism, which renders their usage complex.

In this atmosphere of uncertainty, the simple measure of...
diminishing tobacco usage is itself difficult, and overconsumption of tobacco is regularly observed in this population. The medical management of HIV-infected patients is mostly carried out by infectious disease specialists, and the field of cardiovascular diseases is not usually familiar to them.

The history of AIDS has taught us that phenomena are most quickly and effectively understood when light is cast on them from a variety of angles, using a variety of tools. The dynamism which has always characterized AIDS research will doubtless benefit from greater comprehension of the mechanisms of these poorly understood metabolic disorders.

The present volume contributes to disseminating knowledge in the field so that the various actors can pool their expertise towards a successful management of cardiovascular disease in HIV-infected patients.

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Introduction

The are probably few examples, if any, in the story of medicine like the one concerning the abrupt change that pharmacological research determined in the clinical evolution of HIV infection and AIDS. In few months since the introduction of the first triple drug association deserving the acronym HAART (Highly Active Antiretroviral Therapy), the life expectancy of persons infected with HIV switched from a few years to a still indefinable time that we can today estimate as several decades [1]. Those physicians who are sufficiently aged to have assisted HIV-infected patients both before and after the introduction of HAART, have probably experienced one of the most important events in their life. It is often difficult in these times to make young doctors (and young patients as well) aware of the magnitude of the change that took place in the overall life perspective of humans infected with HIV. While for the newcomers to antiretroviral therapy it is rather natural to see patients’ immunity regain its competence under appropriate antiretroviral treatment, some of us still perceive something like a miracle in watching the reversal of such an otherwise deadly human disease. Most of our concerns today are related to side effects resulting from HAART rather than to its efficacy, and we are increasingly focusing on the long-term therapeutic balance (with issues like toxicity, tolerance and adherence) instead of life-threatening opportunistic infections. A short paragraph on the natural history of HIV infection is thus fully justified in the intention to remind others of how things were, and still are in many geographical regions, before the use of multi-drug therapy transformed HIV infection from a lethal disease to a condition often compatible with a reasonably normal life.

The Natural History of HIV Infection

In the years following the time when specific diagnostic molecular assays became available (HIV serology by means of ELISA and Western-Blot techniques), we eventually recognized the rather atypical clinical evolution of HIV infection. With infectious diseases resulting in physicians being more accustomed (with notable exceptions) to deal with acute disease forms, the multiphasic progression of HIV infection, with long-lasting asymptomatic periods, brought to our attention a totally new infectious disease model.

Well before HIV was identified as the causative agent of AIDS, a clear-cut correlation was established between the downgrading tendency of immune surveillance and the increasingly severe clinical manifestations leading eventually to death [2]. It is worth noting that 26 years after the first five AIDS patients were described as individuals developing unusual opportunistic infections and neoplasms in association to extremely low numbers of circulating CD4+ T-lymphocytes, no immunological markers
better than CD4+ cells have been identified as indicator of immune status in patients with HIV infection [3]. Although exceptions are not so uncommon, the relationship between the CD4+ cell count and the likelihood of developing specific opportunistic diseases is still the best clinical rule for clinicians to rely upon in the diagnostic workup of patients with HIV infection. There are no other human diseases in which the relationship between an immunological marker and a given clinical condition is so coherent. Although the distinction between HIV infection (defined by a positive HIV serology) and AIDS (defined by a positive serology in association with some major associated disorders) is still made on a clinical ground, reliance on the number of circulating CD4+ cells is pivotal in the process of choosing diagnostic procedures and taking therapeutic decisions [4].

Based on these two markers (serology and CD4+ count), a more than approximate description of the natural history of HIV infection can be easily plotted on a graph, with the time elapsing since infection on the x axis and the absolute number of CD4+ T-lymphocytes/μl on the y axis (Fig. 1). In the 2nd half of the 90s, a molecular marker representing the plasma concentration of HIV-specific nucleic acids became available (HIV-RNA), which made it possible to quantify the presence of HIV in the blood and to successfully relate it to clinical and immune disease progression [5].

In clinical terms, the manifestations of HIV infection can be classified in four sequential phases. In the days following infection, an acute inflammatory syndrome may take place with a rather wide variety of signs and symptoms [6]. In more than 50% of symptomatic cases, fever, pharyngitis (“mononucleosis-like syndrome”), systemic adenopathy, cutaneous rash and diffuse musculoskeletal pain are usually present, but less common disease forms are also described, with involvement of the central nervous system [7]. Acute retroviral syndrome tends to subside in a few days to several weeks; and, depending on a variety of circumstantial factors (clinical presentation, physician’s experience), it may actually be recognized or simply interpreted as a common flu-like disease. Today it is common

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**Fig. 1.** The chronological relationship among immunological (CD4+T-cells) and virological (HIV-RNA) markers and the clinical evolution of HIV infection is represented. The red line refers to circulating CD4+T-lymphocytes and the green line refers to plasma HIV-RNA.
practice to rely upon plasma HIV-RNA assays when serology is still negative and the clinical picture suggests the possibility of acute retroviral syndrome. While anti-HIV antibodies may take up to several months to become detectable, the molecular evidence of HIV infection in the plasma well anticipates seroconversion, thus allowing the diagnosis of newly acquired HIV infection in the absence of detectable anti-HIV antibodies [8]. It must be recognized, however, that it is not easy to estimate the rate of newly acquired HIV infection cases producing acute symptomatic disease, and the proportion of newly diagnosed infections presenting with an acute inflammatory disease form is rather low.

After primary infection (which may thus pass unnoticed in a substantial proportion of cases) a prolonged asymptomatic phase follows, which usually lasts several years [9]. With progression of immune decline, an early symptomatic phase may be recognized, with some minor clinical manifestations like pharyngeal candidiasis, systemic lymphadenopathy, seborrhoeic dermatitis [10]. When immune deterioration gets below the threshold of 200 CD4+ T-lymphocytes/μl, the patient enters in the phase of highest vulnerability to opportunistic disorders, as the risk of developing overtly symptomatic opportunistic disorders increases in inverse relationship with decreasing CD4+ T-lymphocytes [11]. The clinical phase corresponding to a CD4+ cell count <200/μl is thus the most symptomatic one and in the vast majority of patients, the clinical diagnosis of AIDS is made with a number of circulating CD4+ T-lymphocytes below such a value. In a minority of patients, however, AIDS-defining clinical manifestations may occur when their CD4+ cell count is still above this threshold, as may be the case with less strict opportunistic disorders like Kaposi's sarcoma, esophageal candidiasis, extrapulmonary tuberculosis or recurrent bacterial pneumonia [12, 13].

Among the major opportunistic infections occurring in patients with less than 200 CD4+ cells/μl, some difference is worth noting. While infections like Pneumocystis jirovecii pneumonia (formerly known as P. carinii pneumonia or PCP) and Toxoplasmosis may take place with any CD4+ cell count below 200/μl (with increasing frequency at lower values, however), some specific opportunistic infections like cryptococcosis, multi-organ disease by Cytomegalovirus, atypical mycobacteriosis or less frequent infections like that from Rhodococcus equi tend to develop in the very latest phase of the downgrading course of HIV-related immune deterioration, such as when the CD4+ cell count has dropped below the value of 50/μl [14]. In clinical practice, the diagnosis of one among these extremely opportunistic disorders corresponds, therefore, to a residual immune competence approaching exhaustion. From this viewpoint, it is worth noting that some increase in the incidence of these end-stage opportunistic infections was seen in the 90s such as when the life expectancy of AIDS patients also increased as a result of a more appropriate and timely management of opportunistic infections (both therapeutic and prophylactic) [15]. In the western world, the improvement over time of the medical ability in the overall management of AIDS patients made it more likely, for a sizeable proportion of them, to survive until their immune competence eventually consisted of only few remaining CD4+ cells. In regions of the world where highly specialized care was not available, opportunistic disorders typical of this very last phase of the HIV clinical course were rarer, since death was more likely to occur in earlier phases.

Furthermore, regarding these specific opportunistic entities, and several other infections and neoplastic diseases also listed among the AIDS-associated conditions, the clinical picture usually also includes constitutional signs and symptoms like significant weight loss (>10% of normal body
A particularly relevant position in the spectrum of the HIV-associated opportunistic infection is that of tuberculosis (TB). Active TB may develop in any human being regardless of the presence of specific immunosuppressant conditions, but as is the case with other predisposing factors, in the case of HIV infection, the risk increases several fold as compared to the general population [19]. In patients with HIV infection, the risk of developing active TB increases when the individual immune surveillance declines and such increased individual vulnerability has been demonstrated both in the case of reactivation of a pre-existing (latent) infection as well as in case of de novo exposure [20, 21]. Further to play the role of the most powerful factor predisposing to active TB, HIV infection was also found to alter the clinical presentation of the disease [22]. In a sizeable proportion of patients with low values of circulating CD4+ cells (<200/μl), the loss of the ability to mount an adequate cellular immune reaction often corresponds to unspecific pathologic pictures, with no or only poorly formed granulomas [23]. In terms of clinical presentation, the lesions appear less distinct from the surrounding parenchyma and the typical cavitations are often absent. This loss of immune control also translates into a higher frequency of extrapulmonary lesions as well as higher numbers of bacilli at the histopathologic level. Since the incidence of TB is closely related to the degree of disease endemicity, it is not surprising that TB represents the most frequent infectious disorder associated to HIV infection in the developing world [24].

The progressive multi-step clinical evolution of HIV infection might not be entirely observed in the individual patient, as is the case in the so-called “late presenters”. This typically happens when subjects who are unaware of being HIV-infected develop a major, AIDS-defining, opportunistic disorder. In these increasingly encountered patients, the silent, asymptomatic loss of immune competence becomes recognizable only when the abrupt development of a totally unexpected opportunistic disorder discloses the diagnosis of AIDS.

In a small minority of patients, who are known as “long-term non-progressors”, HIV infection does not seem to determine the same unfavourable immune deterioration which is described in most patients. Although it is not clear how the eventual outcome of HIV infection will be in these subjects, a number of reports have described a rather steady immunological condition up to 20 years since HIV was acquired [25, 26].

In the years preceding the release of effective antiretroviral regimens, the only therapeutic measures available to counteract the effects of the downgrading tendency of immune surveillance were drugs specifically active against opportunistic pathogens. Further to be used in the treatment of specific opportunistic infections, these drugs were also administered as prophylactic agents both for primary (e.g. for preventing P. jirovecii pneumonia in patients with less than 200 CD4+ T-lymphocytes/μl) or secondary prophylaxis (following the treatment of the first episode of opportunistic infection) of otherwise frequently occurring opportunistic infectious processes [27]. Although neither treatment or prophylaxis were able to reverse the tendency to lose immune competence over time, the life expectancy of HIV-infected patients who were carefully monitored on this basis was significantly increased in the years before HAART became available [15]. It is unclear to what extent the release of the first antiretroviral drugs contributed to this pre-HAART improvement in the life expectancy of AIDS patients. The use of azidothymidine (AZT) alone was found to delay the onset of AIDS, but no advantages were seen in terms of life duration [28].
The Effects of Highly Active Anti-retroviral Therapy (HAART) in the Clinical Aspects of HIV Infection

It took a few months to realize how the use of existing nucleoside analogues inhibitors of the HIV reverse transcriptase (NRTIs) in combination with the newly released protease inhibitors (PIs) was associated to a spectacular reversal of the otherwise inescapable deterioration of immune competence [29, 30]. To better understand the changes that occurred with the introduction of HAART in those years, we must also consider the importance of the concomitant release of the test for measuring the amount of circulating HIV (plasma HIV-RNA by polymerase chain reaction–PCR) [31, 32].

Until that time we were dealing with a poorly active treatment (one or two NRTIs) whose efficacy was rather difficult to establish, since the rise in CD4+ cell count (of scarce extent, if any) took several weeks or months to become apparent and a short time to vanish. In the years preceding the use of HIV-RNA, the measurement of plasma p24 antigen levels, as a surrogate marker of the circulating viral burden, was employed to some extent but it never became part of the routinary analyses in HIV-infected patients, mostly for its limited clinical value [33]. In few months we acquired both much more potent therapeutic weapons and a pharmacodynamic marker more sensitive to treatment effects. Further to produce a quicker and more consistent effect on CD4+ cell count, HAART was also found to determine a rapid drop of logarithmic magnitude of the plasma HIV-RNA, which was demonstrable well before any rise in CD4+ cells [34]. The almost contemporary release of these two new instruments made it thus possible to both effectively treat HIV infection and to monitor treatment effects more timely and precisely than before. With the early evidence of HIV-RNA fall as indicator of therapeutic efficacy, with CD4+ cell increase ensuing thereafter, physicians administering HAART to their patients had thus increased confidence in this new treatment modality. From a more popular perspective, the now fully demonstrable and consistent association taking place between immunovirological and clinical benefit under HAART was the final and definitive answer to those persisting minor rumours against the role of HIV infection in the pathogenesis of AIDS [35]. The importance of relying upon plasma HIV-RNA as early efficacy marker is today emphasized by the common habit of designing short-lasting (10–14 days) phase I therapeutic trials aimed at assessing, as “proof of concept”, the antiretroviral properties of new compounds before proceeding to conventional clinical studies [36].

In the years 1995–1997, with minor delays in some western regions, the introduction of combination therapy consisting of two NRTIs and one of the new PIs, determined a dramatic change in the natural course of HIV infection. In less than 2 years, according to the HIV Outpatient Study, mortality in patients with HIV infection dropped from 29.4 per 100-person-years to 8.8 [1]. In Italy the mortality of AIDS patients (determined as the number of yearly AIDS deaths per number of AIDS diagnoses in the same year) dropped from 67.3% in 1995 to 9.0% in 2005 [37]. A decline of similar magnitude was also seen in terms of lower incidence of opportunistic infections like P. jirovecii pneumonia, CMV retinitis and atypical mycobacteriosis, whose overall rate declined from 21.9 per 100-person-years to 3.7 in the period 1995–1997 [1]. The latter findings gave a working confirmation that immune recovery under HAART was not only numerical but also functional, thus leading to regained effective immune surveillance [38]. This was also testified by the spontaneous recovery from some opportunistic infections (without specific chemotherapy) in patients undergoing...
HAART-associated immune reconstitution, which implies that the sole CD4+ cell increase may be sufficient to get rid of the ongoing active disorder by simply restoring a protective level of immune surveillance [39]. With few exceptions, which are likely to be attributable to some specific clonal deletion in immune reconstitution [40], the number of CD4+ to be restored in order to confer spontaneous protection against opportunistic pathogens was found to be the same as the one established before HAART was available. On this basis, once a patient has undergone a numerical recovery of CD4+ cells known to be sufficient to keep the patient out of a CD4+ defined risk of opportunistic infection, prophylaxis or maintenance therapy against specific opportunistic infections may be safely interrupted [41, 42].

A number of cohort studies have subsequently confirmed the unambiguous and sustained survival advantage provided by HAART. In the years following the astonishing debut of HAART in the HIV scenario, the exciting new wave of pharmaceutical research in antiretrovirals made it also possible to find the appropriate answers to a series of problems emerging from the ordinary antiretroviral practice such as resistance to existing drugs, insufficient antiretroviral potency, side effects and adherence, thus substantially keeping the initial promise of a really effective treatment. The effects of HAART in the clinical manifestations of HIV infection also translated into the emergence of new, HIV-unrelated causes of death in patients with HIV infection [43]. This is to say that concomitant diseases like HCV chronic hepatitis, which were neglected in the pre-HAART era, became a priority in the management of patients with HIV infection. A number of pathophysiological factors well describe the complex pathogenetic interaction of diseases coexisting with HIV, but the single simple fact that HIV-infected patients receiving adequate antiretroviral therapy have many more years to live, clearly implies that these conditions have a longer time to fully develop to clinically significant manifestations.

Today the management of HIV-infected patients has switched from mostly inpatient to mostly outpatient, since the most frequent service to be delivered is that of monitoring efficacy and toxicity of HAART in patients whose average quality of life has greatly improved and who do not require, in most circumstances, to be assisted in the hospital. A sizeable proportion of patients, however, still require intensive hospital-based treatment, as treatment failures occur for a variety of reasons: lack of patients’ adherence to treatment, real treatment failures due to resistance to antiretrovirals, symptomatic chronic virus hepatitis, neoplastic diseases and other concurrent infectious and non-infectious conditions requiring close monitoring (e.g. active tuberculosis). In addition to these occurrences, we have also to face the increasingly important issue of the “late presenters” such as patients who present with a major opportunistic disorder without any prior clinical or serologic evidence of HIV infection. These are truly AIDS patients as we were accustomed to seeing in the pre-HAART era, and require the same therapeutic measures we had been applying in those years. Although HAART may be highly efficacious also in these cases, a measurable rate of early mortality is recorded in these patients, mainly due to the nature of the AIDS-defining disorder they present with.

In Italy, the proportion of new cases of HIV infection meeting the case definition for AIDS increased from 18% in 1995 to nearly 50% in 2005 [37]. The reason why this has happened has probably some epidemiologic reasons, at least in countries like Italy, where the responsibility of sexual transmission as a risk factor for acquiring HIV infection increased from 27.5% in 1995 to 61.7% in 2005, while parenteral transmission among heroin addicts decreased from 66.7% in 1995 to 30.8% in 2005 [37]. Whereas, in
the case of intravenous drug abusers, the outpatient facilities are able to detect HIV infection in earlier stages (as part of the ordinary serologic screening) in the majority of cases, the STD clinics can only screen that minority of the sexually active population who present with some disturbances. Although such a significant switch in HIV epidemiology might only be representative of regions like Italy, France and Spain, the phenomenon of “late presenters” is well present in most western countries. As a consequence, in order to curb this wave of AIDS presenters, efforts should clearly be made in the setting of the screening strategy, since the effectiveness of today’s available HAART might prove to be useless in this not-so sizeable proportion of patients.

Antiretroviral Therapy Today

In late 2007, twenty antiretrovirals are available on the European market, with a further three drugs approaching official release in early 2008. In the last 10 years, by excluding some pharmaceutical remake and dual or triple drug co-formulations of existing drugs, the mean number of new antiretrovirals per year has been 1.5. Today, four drug classes are available (N/NtRTIs, NNRTIs, PIs, entry inhibitors), and a fifth (integrate inhibitors) is about to make its entry in the anti-HIV pharmacopea. Newer drugs classifiable in the existing classes and new classes are also in the pipeline (maturation inhibitors, monoclonal antibodies as entry inhibitors), thus testifying of the exciting liveliness of this pharmaceutical sector, probably the most active branch of pharmaceutical research in these times.

In the years following the first introduction of HAART, the therapeutic strategies underwent several changes on the basis of the new knowledge resulting from clinical evidence and according to the properties of the numerous new drugs that have been released over time. Therapeutic guidelines delivered by national and supranational health authorities (e.g. DHHS in USA and BHIVA in UK) are continuously updated in order to provide the best available indications for the overall management of HIV infection [44, 45].

The basic therapeutic potential of antiretroviral therapy today is that of providing significant inhibition of viral replication and then, as a result of the latter, recovery of CD4+ T-lymphocytes. This translates into clinical recovery in those who are symptomatic and in a condition of clinical stability for patients who begin their treatment while still in the asymptomatic stage. The response rate, which may vary according to numerous factors, may well be over 75% in patients starting HAART, and today numerous alternative options are available for those who do not respond to their first regimen. The most atypical and thorny aspect of HAART is that it must be administered for life. HIV infection is the only infectious disease requiring permanent therapy, as treatment interruption is followed by resumed viral replication, immunological impairment and progressive clinical deterioration, that is to say that HIV infection resumes its natural course. The only analogy may be that of chronic hepatitis B infection, for which, today, continuous suppressive treatment is also being advised [46].

The clinical demand has been changing over time as a consequence of different problems that arose in clinical practice. In the first years following the introduction of HAART, it soon became apparent that HIV was able to change its susceptibility to antiretrovirals and to become drug-resistant in a classic Darwinian way. By applying methods of molecular biology, it was possible to identify genotypic patterns of viral isolates that were correspondent to distinct phenomena of drug resistance. While In Vitro systems for testing viral sensitivity to antiretrovirals (phenotyping) were also developed, viral genotyping was found to be the
most reliable and practical method for guiding antiretroviral selection in the case of resistant infections and today it remains the reference method [47].

A fundamental change in antiretroviral therapy took place when clinical pharmacology studies provided the means to overcome and prevent viral resistance. Among the first PIs released into the market, Ritonavir (RTV, which was subsequently abandoned as pure antiretroviral) was found to display remarkable properties in enhancing the pharmacokinetic (PK) exposure of other PI [48]. Through its interference with the isoenzyme CYP3A4 of the cytochrome P 450 system in the intestine and liver microsomes, RTV (at a daily dosage well lower than that recommended for its use as antiretroviral) was found to be able to increase PIs absorption and to decrease their metabolism, thus eventually leading to PK exposure of the co-administered PI which was up to 3 logs₁₀ higher than in the case of treatment without RTV. Such enhanced PK exposure led to the ability of RTV/PI-based treatments to overcome, to some significant extent, the pre-existing resistance selected by regimens containing a single PI, thus determining successful re-suppression of viral replication in patients who underwent virological failure with a single PI-based therapy. Furthermore, in the following years, it became apparent that the use of RTV/PI-based therapy was also able to almost totally avoid the selection of resistance when administered as first-line treatment in treatment-naïve patients [49]. The effect of this enhanced PK exposure on resistance prevention was found to also include the drugs co-administered with RTV/PI-based regimens, thus providing a benefit, in terms of long-term perspective, which goes far beyond the class of PIs and involves the entire pharmaceutical armamentarium we rely upon today for treating HIV infection. It must be stressed that the confidence we have today in the possibility to find a therapeutic solution for almost all individual patient conditions (e.g. resistance, intolerance, drug-drug interactions, pregnancy, organ failure, etc.) is largely based on the knowledge that RTV-boosted PI-based regimens will provide a concrete chance of therapeutic response in the vast majority of patients, unless very extensive resistance has been selected in the past. In this regard, it is worth noting that the process of multiple drug resistance selection resulting from the use of suboptimal regimens (which took place until the concept of boosting PI-based therapy with low-dose RTV was fully translated into large-scale use) has now come to its end, at least in the western world. This is to say that the use of RTV-boosted PI therapy does not generate the multiple resistance patterns selected by a single PI therapy any longer; and, thus, the size of the HIV-infected population carrying multiple drug resistance should not increase to any significant extent in the future [50].

Most of currently administered HAART regimens consist of two drugs belonging to the N/NtRTIs class (the so called “N/NtRTIs backbone”) and a third drug to be selected among PIs or NNRTIs. When administered to patients in a treatment-naïve status, these regimens have repeatedly been proven to guarantee a long-term immunovirological and clinical benefit—provided they are taken regularly by the patients and no specific interferences are present. In the case of patients who are not eligible for these first-line recommended options because of prior resistance selection, a number of alternatives are available, both within the class of PIs (in the near future also in the class of NNRTIs) and in other newly developed drug classes [44, 45].

Although viral resistance is not the only problem in this therapeutic area, it is nevertheless the one that may definitively compromise the use of a drug class. While PIs are now recognized to be the drug class less vulnerable to resistance selection (in the RTV-boosted version), N/NtRTIs, NNRTIs
and Enfuvirtide (the only entry inhibitor so far available) display various degrees of weakness in terms of genetic barrier. The term genetic barrier substantially indicates the number of mutations required to make HIV resistant to a drug or a drug class. The higher the number of mutations required to determine resistance, the stronger the genetic barrier. With the exception of PIs in association with RTV as a booster, for most of the other drugs, a single mutation (such as even a short exposure) may be sufficient to select for a drug-resistant infection. Considering that cross-resistance among members of the same class is rather common, attention is being increasingly paid to the best sequential strategy to be adopted in planning antiretroviral therapy. What has been learned after years of antiretroviral therapy is that the same principles applied almost 60 years ago in the multi-drug treatment of tuberculosis are also valid for antiretroviral therapy [51]. In other words, once resistance has developed and we have to face treatment failure, no single new active drug should be added to a failing regimen, since selection of resistant mutants will determine the emergence of virions which are also resistant to the newly introduced drug. In all clinical trials carried out to evaluate the effectiveness of new antiretrovirals, the best performances were seen when at least another component of the therapeutic regimen (further to the new experimental drug) was fully active against the virus. With only a single drug being active in any given regimen, the usual therapeutic result is that of a transient immunovirological response (often not complete) followed by a new therapeutic failure. As a consequence, in case of multi-drug failure, the best strategy is to select at least two active components to be included in the new regimen [52].

Side effects, both short and long-term, are another important issue in antiretroviral therapy. There are a number of drug-specific untoward effects to which patients are variably vulnerable [53]. Gastrointestinal reactions and hypertriglyceridaemia are more common with PIs, and among PIs there are effects like jaundice or nephrolythiasis which are attributable to specific drugs (respectively Atazanavir, ATV, and Indinavir, IDV). In this drug class, some differentiation is also worth making between ATV, Tipranavir (TPV) and the rest of the class in terms of disturbances of glucose homeostasis and decrease in insulin sensitivity; the former two, which do not interfere with the cellular receptor GLUT-4, are less prone to determine alterations in this setting. Cutaneous rash is more common with NNRTIs than with PIs, and neuropsychiatric disturbances (especially in the first weeks of treatment) are more common with Efavirenz (EFV) than with any other antiretroviral. Some degree of liver toxicity is attributed to NNRTIs, and their use should be cautious in case of co-existing viral hepatitis. On the side of the current most common “backbone” of HAART (N/NtRTIs), there are some specific reactions in the case of abacavir (ABV, genetically determined vulnerability for developing severe inflammatory reactions), tenofovir (TDF, reversible renal failure with concurrent factors), zidovudine (AZT, anaemia, lipoatrophy), Didanosine (peripheral neuropathy, pancreatitis) and stavudine (d4T, lipoatrophy), while the two citidine analogues lamivudine (3TC) and emtricitabine (FTC) are by far the best tolerated drugs in this class [54]. The outlook of side effects should also be analysed in longer terms such as in years of continuous treatment. In this perspective, complex pictures consisting of various degrees of metabolic and morphologic alterations are known to occur in recipients of antiretroviral therapy. From the metabolic side, disturbances in the glucose and lipid profiles are rather common and may form the basis for interpreting the higher incidence of cardiovascular events recorded in HAART intakers as compared to the age-matched population. While a small class-
specific responsibility seems today to be attributable to PIs as compared to NNRTIs in the increased cardiovascular risk, many other concurrent factors should also be considered in this specific context, since traditional risk factors, like smoking, are also heavily represented in the HIV-infected population [55]. The other side of the coin, however, shows how a higher cardiovascular risk is also measurable in those with lower CD4+ cell counts, which means that in any case, the successful use of HAART is well favourable also in this specific regard [56].

The development of lipodystrophic syndromes (altered distribution of body fat), which have ambiguous links with the metabolic disturbances, is more likely to result from regimens containing d4T or, to a lesser extent, AZT, while the responsibility of other drugs is still sub judice. A recent ACTG trial (ACTG 5142) has actually capsized the belief that lipoatrophy was more common among PIs intakers as compared to NNRTIs; the results showed how the incidence of lipoatrophy was significantly higher in patients taking EFV as compared to those receiving lopinavir/RTV (LPV/r), regardless of the companion drugs also administered [57].

An additional point to consider in the long-term perspective is that of the incidence of non HIV-related diseases in the HIV-infected population. As said for the increased risk of cardiovascular events with lower CD4+ cell counts, the same applies for other conditions like renal failure, non-opportunistic infections and malignancies. This means that, in order to lower the risk of such occurrences over time as far as possible, our immunological target in antiretroviral therapy should be set at levels higher than 350 cells/μl. In the ongoing debate on the best therapeutic strategy for achieving the most convenient balance between treatment efficacy and side effects, this information certainly adds more weight on the side of the favourable effects of antiretroviral therapy [56].

From Now On

It is not easy today to depict which will be the real long-term perspective of HIV infection. There are several major points which deserve careful consideration. One is certainly epidemiology and the future trends of HIV diffusion in the different regions of the world. The major focus here is on developing countries, on the access to appropriate care in these regions and on the global impact that the ongoing preventive and therapeutic efforts will have on HIV epidemiology in the short-, mid- and long-term. Since a few years ago, a considerable amount of resources has been delivered to developing countries for the prevention and treatment of HIV infection, and an additional question relates to how long this will be affordable.

The epidemiologic tendency is also of great concern for western countries, where the extent to which preventive efforts are made is quite variable and there is much uncertainty about the future directions to be undertaken in this setting. The life expectancy of HIV-infected patients increased considerably following the introduction of HAART, a rather constant number of new infections are being diagnosed each year and, as a simple numerical consequence, the perspective is that of a growing proportion of our societies consisting of subjects with HIV infection, which corresponds to a growing number of subjects requiring antiretroviral treatment.

From a more technical viewpoint, that of chemotherapy, the question is whether the newly released antiretroviral drugs and those in the last portion of the pipeline will modify or not the current global treatment perspective. While viral eradication is still far beyond our current possibilities and continuous anti-HIV treatment remains substantially unavoidable, some recent results achieved in the use of new drug classes seem to indicate that our weapons against