The future of antiretroviral therapy: challenges and needs

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The introduction of combination antiretroviral therapy (cART) has substantially modified the natural history of HIV infection. At the beginning of the cART era the objective was focused on HIV-1-associated mortality and morbidity, but as this objective was accomplished other issues emerged, including toxicity, resistance and compliance with treatment. Moreover, the participation of other disease mechanisms, such as proinflammatory activity, in the so-called non-AIDS events is becoming increasingly important. To overcome these issues, therapeutic options have dramatically expanded, which has made the management of HIV-1-infected patients increasingly complex. The intense changes seen raise the question of what will be the future of HIV infection and its treatment. A projection into the future may help to reflect on current limitations, needs and research priorities, to optimize patient care. To debate on this topic a group of 38 experts has initiated The HIV 2020 Project, with the aim of reflecting on the future of HIV infection and identifying the needs that should be the attention of research in different areas. This document summarizes the group’s conclusions on the future of antiretroviral treatment, presented as 20 relevant questions. Each question includes the current status of the topic and our vision for the future.

Keywords: HIV, AIDS, antiretroviral treatment

Introduction

The dramatic and unprecedented benefits resulting from highly active antiretroviral therapy (HAART) have been well described, both on an individual and an epidemiological basis. This has substantially modified the natural history of the disease, and now HIV-1-infected patients live longer and have a better quality of life.

In the early years of the epidemic, the objective was focused on HIV-1-associated mortality and morbidity. However, as the scientific community became aware that HIV-1 infection will turn into a chronic manageable but as yet an incurable disease, other issues emerged. The most important one was the toxicity associated with the long-term use of antiretroviral drugs, and, eventually, its consequences in terms of secondary morbidity and mortality. Evidence has arisen showing the deleterious effects of uncontrolled viral replication, both in patients naïve to antiretroviral drugs and in those who discontinued a successful antiretroviral regimen.

Therapeutic options have dramatically expanded over the last 2 years, and new drugs and new strategies for using them have been developed. This has made the management of HIV-1-infected patients increasingly complex, not only because of expanding therapeutic choices, but also because of the emergence of resistance and the potential for long-term toxicity of antiretroviral agents.

The intense changes seen so far raise the question of what will be the future of HIV infection and its treatment. A projection into the future may help to reflect on current limitations, needs and research priorities, to optimize patient care. To debate on this topic, a group of 38 Spanish experts has initiated The HIV 2020 Project, with the aim of reflecting on the future of HIV infection and identifying the needs that should be the attention of research in different areas. This document summarizes the conclusions on the future of antiretroviral treatment, presented as 20 relevant questions. Each question includes the current status of the topic and our vision for the future.
Objectives of antiretroviral therapy and monitoring of response

1. What will be the objective of antiretroviral therapy?

Current status
Currently, antiretroviral therapy seeks to reduce the viral load to undetectable levels by standard laboratory techniques (HIV RNA of <50, <40 or <20 copies/mL, depending on the method used), so as to achieve the greatest immunological recovery, and reduction of clinical progression and mortality from HIV infection. With currently available drugs, these objectives have been reasonably achieved.

Recent data suggest that persons on antiretroviral therapy may suffer and die from complications not directly related to virological suppression and the quantitative recovery of CD4 cells. The success of antiretroviral therapy seems to go beyond achieving viral loads of <50 copies/mL. Persistent inflammatory activity and immunological activation, probably secondary to residual viral replication, might underlie the development of the so-called non-AIDS-related events, including cardiovascular disorders, liver or kidney disease and cancers, among others.5,6

Future prospects
It is therefore reasonable to imagine that in the future antiretroviral therapy will seek to reduce mortality from any cause, either directly related or not with the immunosuppression associated with HIV infection. Clinical trials will take into account these clinical objectives. Furthermore, it will seek to suppress the evidence of persistent inflammatory activity or immunological activation, if it is confirmed that non-AIDS-related events might be associated with them.

On the other hand, it seems unlikely that antiretroviral therapy will be administered to cure HIV infection, for which other tools seem to be necessary. However, antiretroviral therapy will be administered in conditions that will optimize the role they can have in the potential eradication of the infection.

2. Will the laboratory methods to measure the response to antiretroviral therapy change?

Current status
Currently, the only tools used to evaluate the response to antiretroviral therapy are the CD4 cell count and measurement of the plasma viral load. These parameters have been shown to be useful for predicting clinical benefit, development of resistance and reduction in transmission.

Measurement of the plasma viral load to levels of <1–5 copies/mL has been used in the context of research. However, it is not clear what benefits these levels of detection could provide in routine clinical practice. Current detection thresholds predict non-development of resistance and are associated with a low or negligible risk of transmission, as well as adequate immunological recovery in most patients and a reduction in the clinical progression of HIV infection. There is doubt as to whether more sensitive detection of the plasma viral load would better reflect the absence of viral replication, and that this would be associated with a reduction in inflammatory activity, immunological activation and their clinical consequences, as well as decreased viral persistence in anatomical and cellular reservoirs.

Future prospects
For this reason, it should be evaluated whether routine measurement of the parameters measuring proinflammatory activity (hsRCP, interleukin-6, CCL2 and others) and immunological activation (HLA-DR, CD38, Ki67 and others) helps to improve the prediction of the development of AIDS-related and non-AIDS-related events in patients receiving antiretroviral therapy.

It seems logical, therefore, that future monitoring of the efficacy of antiretroviral therapy will include measurement of the viral load by ultrasensitive techniques, determination of CD4 cell counts, and evaluation of some markers of immunological activation and inflammatory activity.

Initiation of antiretroviral therapy: when and how?

3. What criteria will be used for initiating antiretroviral therapy?

Current status
There is widespread agreement that symptomatic patients, patients with AIDS and patients with low CD4 cell counts (<200 cells/mm³) require antiretroviral therapy. However, the timing of antiretroviral therapy in asymptomatic, chronically infected patients remains unclear, although there is a growing body of evidence advising earlier initiation of therapy. In fact, the most recent guidelines suggest that treatment be initiated for all individuals with a CD4 cell count of <350 cells/mm³. The guidelines also recommend treatment for pregnant women, patients with HIV-1-associated nephropathy and hepatitis B virus (HBV) co-infected patients requiring treatment for HBV infection, irrespective of the CD4 cell count.1–4

In contrast with previous versions, the most recent guidelines no longer identify specific patients for whom treatment is not recommended. Instead, they indicate that the optimal time to initiate therapy in patients who do not fall into one of the categories mentioned remains unclear, although these may be scenarios in which delaying therapy may be reasonable.

Future prospects
Even in the current scenario of antiretroviral therapy, there are many potential reasons for the move towards earlier therapy. These include that current options for initial therapy are highly effective, durable, convenient and, above all, well tolerated, with minimal evidence of long-term toxicity. Studies continue to demonstrate a higher mortality in HIV-1-infected patients, even when CD4 cell counts remain relatively high.11 Multiple cohort studies are now showing benefits associated with therapy initiated when CD4 cell counts are between 350 and 500 cells/mm³ and, in some cases, >500 cells/mm³.12,13 These benefits include decreasing mortality and morbidity from both opportunistic and non-AIDS-defining conditions. Earlier initiation of therapy is sometimes associated with a better response to
therapy, including a greater likelihood of CD4 cell count normalization. In addition, evidence is growing that prolonged exposure to uncontrolled viraemia might lead to a higher rate of complications, especially those that may occur at high CD4 cell counts, such as non-Hodgkin’s lymphoma, some neurological complications of HIV-1 infection, but also complications resulting from immune activation, and that may affect the cardiovascular or renal system. Furthermore, therapy reduces the risk of HIV transmission in sexual partnerships and, thus, it is likely to also have benefits at the population level.

Thus, keeping this horizon in mind, with current and future antiretroviral drugs that are highly effective and have absent or negligible long-term toxicity, therapy will be initiated as soon as patients are diagnosed. In 2020, the most likely question that will arise will be ‘Who should not receive treatment?’ It is most likely that the only non-treated patients will be most of those who are elite controllers or long-term non-progressors, although even some of these patients may show clinical progression and benefit from therapy.

4. How will HIV-infected persons who are candidates for initiating antiretroviral therapy be identified?

Current status

Currently, a significant number of patients (between 30% and 50%) reach the point of care very late in the course of HIV-1 infection. Late presentation is associated with increased morbidity and mortality, increased risk of transmission of HIV, and suboptimal response to therapy. This late presentation is too often a consequence of a late diagnosis and several epidemiological studies have identified that some groups of populations are more likely to be diagnosed late. On the other hand, it has been estimated that ~30% of HIV-infected individuals are undiagnosed due to a restrictive policy of HIV testing in most settings.

Future prospects

If we are to treat all patients from the very beginning of HIV-1 infection, a means of diagnosis must be available for the entire population. However, all these policies need a proper legal framework to be developed to assure universal HIV-1 testing in a given population at their first contact with the health system, followed by the immediate offer of adequate therapy for life, provided that the patient is ready and likely to adhere to therapy. The cost of antiretroviral treatment is a matter of growing concern, since it is rocketing year after year. This may put the sustainability of the entire system in danger.

The potential benefits of a policy of universal testing and treatment are 2-fold. On an individual basis, it is going to increase the quality of life and life expectancy, thus providing the society with an additional labour force. On a population basis, this may potentially bring transmission to a very low level and may ideally put the epidemic to an end. The sole reservoir of the HIV-1 virus is the human being who acts as a carrier and an old aphorism in epidemiology says that ‘…if there are no carriers, there are no cases’.

5. Will three continue to be the magic number of drugs for initial HAART?

Current status

The objective of maximizing the potency of the regimen and minimizing the risk of selection of resistant viral strains has promoted the combined use of three drugs. The historical evolution of the availability of antiretroviral drugs allowed this objective to be initially achieved with the combination of two nucleoside analogues and a protease inhibitor. Subsequently, it was confirmed that this could also be achieved with two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor. This improved the limited potency of single-drug therapy and two-drug therapy with nucleoside analogues, while at the same time increasing the total number of resistance mutations (genetic barrier) that had to be selected for the regimen to cease to be effective.

Two facts, however, will cause this paradigm to cease to exist in the near future. First, the evolution of classic protease inhibitors into ‘boosted’ protease inhibitors. Boosting with low doses of ritonavir improves the pharmacokinetics of these compounds, thus increasing the number of mutations required for the virus to no longer be susceptible to the drug. This number of mutations, or genetic barrier, is equal to or even higher than that required with classic triple therapies. Secondly, the antiviral potency of boosted protease inhibitors and of drugs from other families (non-nucleoside reverse transcriptase inhibitors, integrase inhibitors and CCR5 co-receptor inhibitors) is superior to that of nucleoside analogues.

Future prospects

Taking together these two characteristics (genetic barrier and potency), it is now possible to design combinations of two drugs (including a boosted protease inhibitor) that combine both equal or greater potency and genetic barrier than the triple drug combinations including two nucleoside analogues and a third drug. This type of combination is now being tested in clinical trials and it is expected that their clinical utility will be confirmed. However, the availability of dual regimens with these characteristics does not mean the disappearance of triple therapies, since the degree of simplification achieved (two nucleosides and a non-nucleoside in a single once-daily tablet) makes them difficult to surpass in ease of use.

6. Will we go back to using a single drug?

Current status

The high potency and genetic barrier currently achieved with the combination of drugs is not readily achievable with a single drug. However, ritonavir-boosted protease inhibitors possess both characteristics, so they can be used as monotherapy in certain circumstances. The response rate obtained in naive patients with monotherapy based on boosted protease inhibitors is quite high, but not that achieved with combination therapy.

Future prospects

The lower efficacy of initial treatment with boosted protease inhibitor monotherapy compared with multiple drug regimens,
together with the increasing number of options available for combination using new families of drugs, will make this strategy remain, in the best of cases, a minority option. Nevertheless, it does seem clear that it is unthinkable to use monotherapy with drugs from families other than the boosted protease inhibitors.

7. Will there be a place in initial treatment for combinations of more than three drugs?

Current status
From the perspective of virological efficacy, triple combinations (and, probably, some dual drug regimens) achieve response rates of close to 100%. Initial treatment failures are therefore rarely due to a lack of virological response and their occurrence is usually the result of problems with adherence or tolerance. The addition of more drugs, far from solving these limitations (adherence and tolerance), may increase them. There is currently no regimen with four or more drugs that has surpassed the virological efficacy of triple therapies and it is unlikely that they will do so in the future.

Future prospects
It is unlikely that combinations of more than three drugs will be used in initial treatment to obtain clinical benefits. The door remains open, however, for more ambitious goals than mere virological control to be pursued in coming years, such as a more rapid immunological recovery, control of inflammatory activation (responsible for the problems of co-morbidity in patients with virological control), reduction of residual ongoing viral replication and, even, eradication of the infection. It is possible that to make progress towards these new goals, some combinations with a greater number of drugs, and possibly not all directed against HIV, may provide additional advantages.

8. In the case of three drug regimens, will two nucleosides plus a third drug still be used as standard therapy?

Current status
At present, the use of two nucleosides plus a non-nucleoside or a protease inhibitor is promoted by the possibility of using co-formulations of two nucleoside analogues or even with efavirenz. However, there is much concern among clinicians about the long-term toxicities associated with nucleoside therapy. Abacavir has been associated with an increased risk of suffering cardiovascular events, and tenofovir can cause proximal tubule dysfunction, nephrotoxicity and osteopenia. The importance of these adverse effects may increase in the future, due to the progressive ageing of HIV-infected patients. The only nucleosides that have not so far been associated with relevant toxicity are lamivudine and emtricitabine. It is possible that these two nucleosides will continue to be used in the mid- and long-term.

Future prospects
It is likely that the standard use of two nucleosides as the backbone of initial treatment will change in the mid-term. It is likely that current and future combinations of nucleosides and non-nucleosides as a single tablet administered once daily will continue to be used in coming years, mainly due to its efficacy and simplicity of use. When considering the use of nucleoside-sparing regimens, the importance of studying the efficacy of these regimens for virological control in the genital and central nervous system reservoirs should be stressed.

9. What nucleoside-sparing combinations will be used when the patient is going to receive a boosted protease inhibitor?

Current status
The high genetic barrier of boosted protease inhibitors allows multiple combinations of antiretroviral drugs to be made. However, very few of these combinations have been explored to date.

Future prospects
In naive patients without resistance mutations in the protease gene, the following combinations are likely to be effective:

(i) Boosted protease inhibitor plus non-nucleoside. It is the only combination that has been tested to date (clinical trial ACTG 5142). In terms of virological control, this regimen was not inferior to the combination of two nucleosides plus the protease inhibitor used in the study (lopinavir). This result supports the probable efficacy of different combinations including a protease inhibitor and a non-nucleoside in naive patients.

(ii) Boosted protease inhibitor plus lamivudine or emtricitabine. There are no data on this combination. It has the advantage that both lamivudine and emtricitabine have a good safety profile, and in the case of lamivudine may have clear economic advantages.

(iii) Boosted protease inhibitor plus raltegravir or other integrase inhibitors. Studies evaluating this combination are ongoing (NEAT 001 study, evaluating the combination of boosted darunavir plus raltegravir, as an example) and preliminary data suggest high efficacy with some of these combinations.

(iv) Boosted protease inhibitor plus maraviroc. In naive patients, the early use of CCR5 co-receptor antagonists makes sense, because it is in the early phases that CCR5-tropic viral strains predominates. In addition, the favourable pharmacokinetic interaction between these agents enhances maraviroc exposure, thus allowing a reduced maraviroc dose and, potentially, a once daily administration. However, efficacy and safety data on this combination are lacking at this moment.

10. What nucleoside-sparing combinations will be used when the patient is not going to receive a boosted protease inhibitor?

Current status
There are very few data, at present, on the possible use of nucleoside-sparing combinations not including boosted protease inhibitors. There are many doubts about the genetic barrier of these combinations.
Future prospects
Studies are being initiated with the combination of atazanavir and raltegravir. This regimen is attractive, because it spares both ritonavir and nucleosides. Furthermore, atazanavir increases the plasma levels of raltegravir (although the clinical benefit of this interaction remains to be proven). As for other possible combinations, such as an integrase inhibitor plus a non-nucleoside (etravirine or rilpivirine) plus a CCR5 co-receptor inhibitor, many studies will be needed to characterize their genetic barrier and toxicity profile.

Simplification of antiretroviral therapy

11. Will simplification of antiretroviral therapy be a standard strategy?

Current status
The concept of treatment simplification was coined to designate treatment changes in persons with controlled viral loads aimed at reducing the number of pills and/or daily doses, so as to improve adherence and quality of life. The utility of the strategy has been demonstrated primarily for changing complex treatments including protease inhibitors to other simple ones based on non-nucleosides.

Future prospects
The simplicity and convenience of initial treatments will make classic simplification strategies unnecessary. Furthermore, patients who initiated complex treatments will have them simplified. The possibility of taking one or two fewer pills a day does not seem to be a sufficient reason for changing some drugs for others, unless this has other additional benefits. As far as possible, once-daily regimens will be used from the start.

It is likely that the pharmaceutical formulation of some drugs will continue to improve. More compact dosage forms will allow the number of pills to be reduced and fixed-dose combinations of different drugs will allow treatment to be simplified, but without a change in their composition. It is also very likely that new drugs, including those currently administered in two daily doses (e.g. etravirine, raltegravir and maraviroc), may be administered in a single daily dose, at least in certain patients, if pharmacokinetic data confirm the validity of this approach.

12. In what situations will a change in treatment be indicated in patients with an undetectable viral load?

Current status
In addition to simplifying treatment, most treatment changes in patients with a controlled viral load are made because of poor tolerability or toxicity, or because of adverse clinical or laboratory effects (e.g. gastrointestinal disturbances, lipids or cardiovascular risk). In these cases, some drugs are substituted by others from the same or different families.

Future prospects
Changes due to drug toxicities will certainly continue to be necessary. In addition, it is very likely that some of the induction–maintenance strategies currently under study will be successful. Thus, treatment will be initiated with a greater number of drugs and after a certain time with an undetectable viral load, some of them will be eliminated. As in the case of initial treatment, this strategy could include combinations without nucleos(t)ide analogues, with a boosted protease inhibitor and a drug from another family (e.g. nucleoside, non-nucleoside, integrase inhibitor or CCR5 co-receptor antagonist). Some patients could benefit from the administration of a boosted protease inhibitor as monotherapy. Patients with no previous virological failures and no protease inhibitor-related mutations are those most likely to be switched to a protease-inhibitor monotherapy regimen. Cost reduction is the most significant advantage of such a strategy.

Treatment failure and salvage therapy

13. How will treatment failure be defined?

Current status
Antiretroviral treatment failure can be defined virologically (viral load has not achieved undetectable levels 24 weeks after starting treatment or load has been detected on two consecutive determinations after a previously undetectable level) or immunologically (lack of recovery of the immune system after controlling viral replication).

Future prospects
As mentioned in the previous paragraphs, HIV replication below the level of detection of currently available techniques is not associated with viral evolution and, furthermore, is accompanied by recovery of the immune response in most patients. It does not seem appropriate, therefore, to redefine virological failure using residual viral load thresholds below this figure. Other potential markers of antiviral activity (markers of immune activation or proinflammatory activity), while they may be useful for other purposes, will also not change the criteria for virological failure.

14. How will treatment be chosen for patients who have failed? Will resistance tests continue to be used?

Current status
When a virological failure is documented, treatment should be modified by introducing at least two or, better, three drugs that are fully active. Currently, the choice of antiretroviral treatment in a patient who has failed is largely based on the use of genotypic resistance tests. The technical limitations of these resistance tests make consideration of the patient’s drug history a fundamental tool. Other proposed determinations, such as monitoring of drug plasma levels or viral replicative capacity, are useful in a limited number of patients. Determination of viral tropism is being increasingly used to decide on the potential inclusion of CCR5 antagonists in the treatment of patients on virological failure.

Future prospects
It will be useful and necessary to continue performing resistance tests for at least three reasons: (i) some new drugs from existing
families do have a certain degree of cross-resistance; (ii) it is possible that patients who fail salvage regimens with new families will need to recycle previously used drugs; and (iii) in some cases, drug resistance tests unveil the absence of any significant resistance to failing drugs, thus avoiding the use of newer drugs and allowing the physician to focus on adherence rather than on the construction of complex salvage regimens. Regarding tropism assays, current phenotypic testing will clearly be replaced by the easier-to-perform genotypic tropism assays or other methods that will overcome the many inconveniences of phenotyping.

15. What resistance tests will be used and how will they be interpreted?

Current status

Genotypic resistance tests are currently only used for making clinical decisions. However, these tests have important technical limitations and interpretation difficulties, making them a poor reflection of the treatment history. In fact, they are not useful unless accompanied by a meticulous history of previously received antiretroviral treatments and their results. It is difficult to obtain reliable results in patients with low viral loads (<500–1000 copies/mL) and, furthermore, resistance tests do not allow archived mutations against drugs that the patient failed in the past to be detected. As for their interpretation, different scores have been generated for the same drugs and these also change over time, creating distrust in the clinician, and not always remaining closely related to virological and clinical results.

Future prospects

Genotypic resistance tests will continue to be used, but phenotypic tests will not. Resistance tests should become more sensitive and specific, solving some current problems. Resistance tests should be able to be performed in patients with virological failure with any level of viraemia (>50 copies/mL) and they should be able to access archived mutations using more sensitive techniques to study minority populations. This approach will be clinically relevant for low genetic barrier combinations. While it is already showing that it is useful and has clinical impact in naive patients who have archived non-nucleoside reverse transcriptase inhibitor mutations detected by ultrasensitive pyrosequencing techniques, it is unlikely that it will have clinical impact for boosted protease inhibitor based combinations.\textsuperscript{51,42} Interpretation systems should be based on a robust correlation with clinical variables and should ideally be able to interpret the behaviour of specific combinations or regimens, instead of individual drugs.

16. Will three active drugs continue to be used in salvage therapy?

Current status

In parallel to the recommendations for initial treatment and based on the clinical trials of patients with one or more treatment failures, the salvage therapy of choice should include three fully active drugs.\textsuperscript{43–46} In all the trials conducted, the rate of virological response with three active drugs was uniformly higher than the rate seen with only two active drugs. However, in all the currently available trials, active drugs were mainly recycled nucleoside reverse transcriptase inhibitors and protease inhibitors, enfuvirtide or drugs with some degree of cross-resistance (like new protease inhibitors or etravirine). It is currently unknown if this will remain true with the simultaneous availability of new drugs from old or new families.\textsuperscript{45–51}

Future prospects

Based on the available data, three active drugs will continue to be necessary to treat most patients with previous failures, especially in multiexperienced patients.\textsuperscript{59–52} However, as in other previously mentioned contexts, it will probably be of much interest to reduce the number of drugs in patients with mild or moderate resistance to antiretroviral drugs and good prognostic characteristics (e.g. high CD4 counts and low viral load), using a combination of two drugs that jointly have a high genetic barrier (e.g. a boosted protease inhibitor and another potent drug such as etravirine, maraviroc or raltegravir). This will require that the outcome of clinical trials demonstrating that these combinations are as effective as the current standard is available.

17. What antiretroviral drugs will be important in salvage therapy?

Current status

Management of patients with treatment failure includes the use of drugs belonging to previously administered families (generally, reverse transcriptase nucleoside analogues, and non-nucleoside analogues and protease inhibitors), chosen on the basis of resistance testing, and the incorporation of drugs from new families. With these combinations, a very significant reduction in the number of patients with persistent virological failure has been achieved.\textsuperscript{45–52}

Future prospects

The presence of recycled drugs in salvage therapy will be part of future strategies, at least to the extent to which they continue to be used today. This is particularly true for nucleoside analogues, because of the frequency of cross-resistance between different drugs and the associated potential toxicity. The nucleoside analogues that remain active will be reserved for use in more advanced salvage therapies.

It seems likely that boosted protease inhibitors will continue to be a mainstay in salvage therapy, mainly because their high genetic barrier maintains their activity, even after failure. The availability of new protease inhibitor boosters other than ritonavir and the use of new co-formulations of ritonavir may contribute to this trend.\textsuperscript{53,54} Boosted protease inhibitor-sparing combinations will be the exception in this context, despite the availability of new drugs and families that would allow protease inhibitor-free combinations.
18. How will immunological failure be managed?

Current status

There are no recommendations of proven utility for the management of immunological failure. It is necessary, of course, to exclude causes of lymphopenia that could explain the lack of immunological recovery despite virological control (advanced liver disease, bone marrow invasion by tumors or opportunistic infections etc.). Antiretroviral drugs should also be reviewed. A change should be considered for those drugs that are potentially myelotoxic (zidovudine) or for combinations that have been associated with a lack of immunological response (didanosine + tenofovir, didanosine + abacavir). In the absence of these measures, there are no treatments directed specifically to boost CD4 cells. Recent results on the lack of efficacy of the administration of interleukin-2 were disappointing. 55

Future prospects

The enormous interest that is being focused on the lack of adequate immunological reconstitution in patients with good virological control should bear fruit in the near future. The potential beneficial activity of some antiretroviral drugs in this respect is being evaluated, both in terms of quantitative (increased CD4 count) and qualitative (decreased immune activation of CD4 and CD8) recovery, but there are still no definitive data. It is likely that this research will yield results in the near future, and that drugs will be available that ensure quantitative and qualitative immune reconstitution.

Overall considerations

19. Will new drugs be needed?

Current status

In the last 2 years, there has been an authentic second revolution in the history of antiretroviral treatment (the first was the introduction of triple combination therapy). The nearly simultaneous incorporation of four new drugs, two of them belonging to new families directed towards new targets, has allowed the vast majority of patients in the clinics where these drugs are available to be treated successfully. Both patients initiating treatment and those already on treatment who require changes, because of toxicity, failure or simply with the intent of simplification, have multiple and excellent options. Most needs have been satisfied. The margin for improvement seems small.

Future prospects

It can be understood from the above that there are some areas in which the available drugs do not seem adequate. Some of the patients currently controlled will fail, including failures with new drug families, and will require new drugs and new families, without cross-resistances, for adequate treatment. The problems associated with immunological reconstitution, which even with current treatments occur in a large proportion of patients, require the incorporation of drugs, antiretroviral or not, that help to control the problem.

20. Will it be possible to cure HIV infection?

Current status

Eradication of HIV and cure of the disease are not considered feasible in the short-term. There are multiple barriers that prevent the definitive elimination of the virus. The latent state in which HIV may remain in long half-life memory T cells has been identified as the main obstacle for eradication. But, in addition, it is likely that the residual replicative activity of HIV despite suppressive therapy, anatomical reservoirs and some cells that have yet to be identified will hinder the achievement of this long-sought goal. None of the studies conducted to date in this regard have shown encouraging results. 56

Future prospects

Research on the eradication of HIV has been limited to a large extent by the need to advance the clinical control of the disease. Most efforts have been directed to developing drugs that are effective and well tolerated, so as to prevent suffering and mortality. At present, a large part of the clinical goals have been met and now is probably the time to activate research towards definitive solutions. One of the lines of research is seeking to improve the knowledge of the mechanisms that enable HIV to remain latent and the drugs that could inhibit it. Clinical trials of intensification with new drugs have been initiated, whose results are beginning to appear. Experts in this field demand organizational structures of cooperation to achieve advances in the area. 7 There is the will and the capacity; we only need to wait for the results, which will hopefully be available in the not too distant future.

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**References**


