



HIV/AIDS Treatment

EDCTP Stakeholders' meeting

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Author(s) :

Cynthia Naus, Marjolein Robijn

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1. Introduction

The EDCTP stakeholders' meeting on HIV/AIDS treatment is the third stakeholders' meeting. It was organised by EDCTP together with Spain and hosted by the Instituto de Salud Carlos III, Department of International Research Programs and Institutional Relations in Madrid.

The aim of the meeting was to make recommendations to EDCTP in terms of suitable products in the pipeline for clinical trials; to identify potential sites in Africa to conduct the trials; to identify the capacity strengthening needs for the conduct of clinical trials in Africa. Furthermore, EDCTP would like the meeting to formulate an advice on the funding procedure that should be applied to meet these aims. In addition, EDCTP would like to have a first impression of the financial commitment of the EDCTP-EEIG Member States for clinical trials on HIV treatment.

The meeting was chaired by Prof. Robert Murphy. Professor Murphy works at the Division of Infection Diseases at Northwestern University, Chicago. He has an extensive publication list on clinical trials on anti-retroviral (ARV) treatment and is considered to be one of the main American experts on HIV treatment.

2. Overview participating organisations

2.1 African Network for Care of Children Affected by HIV/AIDS (ANECCA)

ANECCA was established in 2001 in response to the growing recognition that in Africa, the needs of children affected by HIV/AIDS had largely been neglected. To address this problem, ANECCA brings together clinicians and social scientists committed to finding ways of improving the quality of clinical and non-clinical care of children affected by HIV/AIDS, in the Africa region. The Network efforts are targeted at tapping into existing local resources to increase access to, and improving the quality of care provided to HIV affected children in Africa.

More information on the activities of ANECCA can be found at:
<http://www.anecca.org>

2.2 African Regional Capacity Building Network for HIV/AIDS Prevention, Treatment and Care (ARCAN) Project

ARCAN is an African regional capacity building network for HIV/AIDS prevention, treatment and care. ARCAN is active in Kenya, Tanzania and Ethiopia. They organise short term training courses for health care professionals, perform monitoring and evaluation studies and coordinate programmes on HIV treatment.

2.3 EuropeHIVResistance

This European Cohort Coordinating Network on HIV Drug Resistance is an HIV drug resistance surveillance programme funded by the European Commission. It is a network of virological reference centres in 32 European countries, which aims to create an easy accessible platform for the exchange of knowledge and technology throughout Europe. It will also improve the exchange of good practices between the

HIV/AIDS cohorts in Europe. In addition, they seek active collaboration with the other European HIV/Aids cohorts.

More information about the EuropeHIVResistance Project can be found at: http://ec.europa.eu/research/health/poverty-diseases/projects/114_en.htm

2.4 European Commission (EC)

The European Commission is the main funder of EDCTP through Article 169 of the European Treaty. The EC was present by a representative of the Directorate-General for Research. Additionally an EC representative reviewing the EDCTP initiative attended the meeting.

The Infectious Diseases Unit within Research Directorate General is funding research aimed at combating the three major killer diseases (HIV/AIDS, Tuberculosis, and Malaria). They do this through the development of new promising candidate vaccines and therapies, sponsoring research on the full spectrum from basic molecular research through preclinical tests and proof-of-principle on Poverty-related Diseases and through the EDCTP initiative.

More information about goals and activities of the European Commission can be found at: http://ec.europa.eu/index_en.htm

2.5 European and Developing Countries Clinical Trials Partnership (EDCTP)

EDCTP was represented through the Member State Representatives, The Partnership Board (PB), The Developing Countries Coordinating Committee (DCCC), the Executive Director and the Secretariat.

More information on EDCTP can be found at: <http://www.edctp.org>

2.6 Paediatric European Network for Treatment AIDS (PENTA)

PENTA is a collaboration between paediatric HIV centres in Europe and aims to undertake trials in HIV-infected children addressing questions on antiretroviral drugs specific to children, which cannot be answered in adults. PENTA has established a network of over 80 paediatric centres and collaborating laboratories from 13 European (2 Latin American and 1 Asian) countries able to recruit and follow up HIV-infected children in clinical trials to good clinical practice (GCP) standards. May 2007 they have completed 7 trials and have 3 ongoing and 3 in the pipeline. More than 1200 children have been enrolled in major studies coordinated by the MRC Clinical Trial Unit in London, the INSERM/ANRS HIV trial centre in Paris and the Department of Paediatrics at the University of Padova

More information on PENTA can be found at <http://www.pentatrials.org>

2.7 Member State representatives

Each European Member State was invited to send two representatives; the legal European Network Office for EDCTP together with one researcher representing TB treatment research of that specific Member State.

The following organisations represented the European Member States (divide between researchers and governmental representatives):

2.7.1 Agence Nationale de Recherche sur le SIDA et les Hépatites virales (ANRS) - France

The ANRS funds research on HIV/AIDS as well as Hepatitis B and C in France and in Developing Countries. It settles the scientific priorities to be funded and select the programmes.

More information on ANRS can be found at <http://www.anrs.fr/>

2.7.2 Carlos III Health Institute (ISCIII) – Spain

A national public research and scientific support organisation responsible for promoting biomedical and health science research. Its mission is to develop and provide the highest quality scientific-technical services to the National Healthcare System and society in general.

More information on ISCIII can be found at <http://www.isciii.es>

2.7.3 Subdirección General de Evaluación y Fomento de la Investigación (SGEFI- ISCIII) - Spain

The biomedical and healthcare research funded by the Carlos III Health Institute, through the General Sub-Department for the Evaluation and Promotion of Research is part of the National Scientific Research, Development, and Technological Innovation 2004-2007 Plan. This scientific and technological policy instrument of the General State Administration fosters coordination with the Autonomous Regions, and synergies with the Structural Funds and the E.U. Framework Programme. Evaluation of Healthcare Technologies stems from the Spanish National Healthcare System's need to have objective evidence on the medical, economic, social, and ethical impact of medical-healthcare techniques and procedures as one of the foundations for:

- Contributing to the formulation of policies and the decision-making process aimed at the orderly implementation of these in clinical practice when it relates to new policies.
- If already established techniques and procedures, focus their appropriate use.

2.7.4 Clinical Trial Unit (CTU) MRC - UK

The CTU is a centre for clinical research which is supported by the Medical Research Council (MRC) UK. The Medical Research Council is a non-governmental public body whose purpose is to encourage and support high quality research with the aim of improving and maintaining the health of the public and of contributing to national health and quality of life. Randomised Controlled Trials have been a major focus of MRC research for over 50 years and they represent the gold standard in the assessment of new approaches to prevention and treatment in many areas of medicine. Randomised controlled trials (RCTs) are fundamental to evidence-based health care. The vision of the MRC Clinical Trials Unit (CTU) is that all treatment decisions should be based on robust evidence and that if such evidence is lacking, there should be an appropriate trial for patients to join, if they wish. Our goal is to take a lead in providing evidence through the design and conduct of high quality RCTs, systematic reviews and meta-analyses and related epidemiological studies.

More information on the MRC UK can be found at <http://www.mrc.ac.uk>

2.7.5 Federal Ministry for Education and Research, "Health Research" - Germany

The causes of about two thirds of all diseases still cannot be cured. This means that at the best only the symptoms of most diseases can be treated, and even this is not possible with some diseases. Health research is therefore of great importance. Today new or improved methods of diagnosis and therapies are being developed to help sick people more effectively. And new approaches and methods of prevention are being sought so that diseases do not develop in the first place.

More information on the Federal Ministry for Education and Research can be found at <http://www.bmbf.de>

2.7.6 Institute of Tropical Medicine Antwerp (ITM) - Belgium

The Prince Leopold Institute of Tropical Medicine in Antwerp, Belgium (ITM) is one of the world's leading institutes for training, research and assistance in tropical medicine and health care in developing countries. The ITM works with its partners all over the world towards a common goal of "Health Care for All".

More information on the Institute of Tropical Medicine Antwerp can be found at <http://www.itg.be/itg/>

2.7.7 National Centre for Pharmacoeconomics (NCPE) - Ireland

The National Centre for Pharmacoeconomics (NCPE) was established in Ireland in 1998 and is funded by the Dept. of Health and Children. The aim of the centre is to promote expertise in Ireland for the advancement of the discipline of pharmacoeconomics through practice, research and education. Activities of the centre include economic evaluation of pharmaceutical products and the development of cost effective prescribing. The NCPE has academic affiliations with the Faculty of Health Sciences in Trinity College Dublin and is located in St. James's Hospital, Dublin.

More information on the activities of NCPE can be found at: <http://www.ncpe.ie/>

2.7.8 Norwegian Research Council - Norway

The Research Council of Norway is a national strategic and funding agency for research activities. The Council serves as a chief source of advice on and input into research policy for the Norwegian Government, the central government administration and the overall research community. The Research Council works together with research institutions as well as the private and public sectors to enhance financial and quality targets in Norwegian research and innovation activities. It is the task of the Research Council to identify Norway's research needs and recommend national priorities. The Council utilises specifically-targeted funding schemes to help translate national research policy goals into action.

More information about the Norwegian Research Council can be found at: <http://www.forskningsradet.no>

3. Science and products

Prof. Jose de Miro of the Infectious Disease Service of the University of Barcelona presented an overview on the currently approved and new antiretroviral drugs. The presentation was based on the GESIDA/Spanish AIDS plan on antiretroviral therapy in adults infected by HIV; however, these are in general similar to the recommendations of other European countries.

In short, currently three classes of antiretroviral drugs are recognised: First class: the Reverse Transcriptase Inhibitors consisting of: nucleoside analogue reverse transcriptase inhibitors (NRTI), nucleotide analogue reverse transcriptase Inhibitors (NtRTI) and non-nucleoside analogue reverse transcriptase inhibitors (NNRTI). Second class: the Protease Inhibitors (PI) and third class: the Fusion Inhibitors (FI). Currently, the treatment of choice for chronic HIV infection is a combination of three drugs of two different classes or subclasses, including two nucleosides or nucleotide analogues plus one non-nucleoside (NNRTI) or 1 boosted protease inhibitor (PI/r). Initiation of anti-retroviral therapy (ART) is currently recommended in patients with symptomatic HIV infection or in asymptomatic patients on the basis of CD4+ lymphocyte counts (< 200-350 cells/l) and plasma viral load.

New antiretrovirals are being developed targeting different stages of the replication process; Integrase Inhibitors (II) and Maturation Inhibitors (MI). Additionally new types of Entry Inhibitors based on the CXCR4 or CCR5 receptors are in the pipeline; however, these drugs will not be available for the market until 2007-2010. The aim of

targeting new steps in the HIV replication cycle is to develop drugs with safer profiles and with activity against virus resistant to the currently available ARVs.

Two different types of HIV epidemics are recognised: The epidemic in the high income countries where more than 75% of the patients has access to HAART and the situation in the low income countries where less than 10% of the patients with HIV can be treated. This big difference is also demonstrated by the fact that more than 47 different first-line regimens are used to treat 90% of the patients in Europe, whereas only 3 first-line regimens are available in Africa. Moreover the HIV patients in Africa have more severe immune suppression expressed by lower CD 4 counts.

3.1 Overview presented products

As many new antiretroviral drugs are being developed, not all were discussed. The table below only lists some more promising agents that were discussed in more detail during the presentation of Prof. Jose de Miro.

Name of Product	Type	Where in pipeline	Availability	Line of treatment	Tiered price
<i>Etravirine</i> (TMC 125)	NNRTI	Phase III	approval expected 2007	Second or third line	Unknown
<i>Rilpivirine</i> (TMC 278)	NNRTI	Phase II (versus Efavirenz)	2008	First and second line	Unknown
<i>Darunavir</i> (TMC 114)	PI	Phase III finished (darunavir +low-dose ritonavir) <i>Clotet B, Lancet Apr 2007</i>	2006	Second or third line	Unknown
<i>CCR5 inhibitors - Maraviroc</i>	EI - Co receptors	Phase III (2 different doses tested, results similar)	Approval expected 2007	First and second line	Unknown
<i>Raltegravir</i> (MK 0581)	Integrase Inhibitors	Phase III (versus Efavirenz)	Approval expected 2007	First and second line	Unknown
<i>Elvitegravir</i> (GS 9137)	Integrase Inhibitors		Approval expected 2008/2009	First and second line	Unknown

3.2 Needs identified

- As many different drugs are already available in Western countries the discussion focussed more on whether to study first or second line treatment. It was noted that the switch from first to second line treatment is difficult in Africa. In the first

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place it is difficult to get individuals to switch and when this is done, it is often very late. There is paucity of data available on resistance after late switching, but it is observed that in most cases second line treatment is still working even after late switching. Boosted PIs were mentioned as potential second line treatment. This kind of treatment is known to offer protection but a full arsenal needs to be used otherwise the risk of resistance increases. It was noted however that currently tablets for the boosted PI treatment need refrigeration. Ideally tablets should be stable at room temperature. Another issue with switch from first to second line treatment is the involvement of local authorities and regulatory approval of relevant authorities in the country.

- It was observed that patients in the western world have access to over 50 combinations of therapy whereas in Africa only 3 combinations are available.
- It was recommended that EDCTP should try to partner with industry. Some companies such as Gilead, Boehringer, BMS, Roche, Tibotec and Merck are known to be very forthcoming to collaborations with the public sector: however, it was also observed that companies like to control products themselves during the development phases.
- Results of a workshop recently held in Uganda involving 7 African countries were briefly presented. The main needs identified from this meeting were the need for small PK studies in children using existing drugs. In addition the questions when to start HIV treatment, when to switch to second line treatment and what to switch to need to be addressed.
- The switch to other products from the widely used drug stavudine (d4T), which is commonly used as first line treatment because it is very inexpensive; however it is well known that stavudine is one of the most toxic drugs used to treat HIV. Virtually all patients ultimately will develop toxicity to stavudine.
- Support of trials using drugs that are still in developmental stages were discussed and the ethical issue of who will take over treatment after the trial has finished was raised. The EC recommended that EDCTP should focus on phase IV trials.

3.3 Summary of discussion on products and science

At the meeting the needs identified as priority areas for research and development were the key-recommendations made. In response to the chair's request, attendants gave their top 3 priorities, which (summarised) resulted in the following:

The two top priorities are:

1. Paediatrics formulations

The lack of available guidelines and drug formulations specifically for children and adolescents was identified as the top priority. PK studies and fixed-dose combinations were among the top priority.

2. Second line drugs

It was generally agreed that EDCTP should prioritise on clinical trials for second line drugs, which include the development of new second line drugs as well as strategic studies among specific groups. Specifically the questions when to switch from first to second line treatment and which products to switch to need to be addressed, with the latter monitoring resistance is an issue to consider.

New second line drugs were defined as licensed drugs that are not yet available or applicable in Africa as well as drugs that are still awaiting regulatory approval and are currently being tested as potential new first line medication with good resistance profiles (and specific for HIV2).

Other topics mentioned were:

3. Severe disease. A gap in knowledge was identified on the treatment of the severe advanced stages of AIDS, the very sick people. African patients typically present with more advanced disease than their counterparts in the West.
4. HIV-TB. It was generally agreed that TB can hardly be seen separate from HIV in Africa and that studies should be performed in HIV and TB co-infected populations (especially in children). TB patients with HIV should definitely be included in the study, however, specific questions around this issue such as drug-drug interactions should be addressed in a different budget.
5. In the development of new intervention strategies, fixed dose combinations and development of new boosted PI's as monotherapy were prioritised.
6. Mother to child transmission of HIV (MTCT). Improved prevention of MTCT was the last mentioned topic, however since EDCTP has recently funded several proposals on this topic it was not considered a funding priority.
7. Trials on prophylactic drugs for HIV, for instance using tenofovir for pre or post-exposure prophylaxis.
8. Treatment of other co-infections, such as hepatitis B and hepatitis C.

4. Needs in Africa

4.1 Presented needs in the field of HIV treatment

Prof. Souleymane Mboup presented the HIV/AIDS treatment needs in Africa. Regional HIV/AIDS statistics show that in 2006 in sub-Saharan Africa, 24.7 million adults and children were living with HIV; while 2.8 million got newly infected that year and 2.1 million people died. The coverage of antiretroviral therapy in sub-Saharan Africa was an estimated 23% in June 2006. Children have even less access to HIV treatment. These figures show that there is an urgent need for people to get better access to ARV Therapy. Moreover, fewer first line regimens are available for the patients in sub-Saharan Africa (3 regimens) than for patients in Europe (47 regimens) and North America (59 regimens). The adherence in Africa strongly varies per country, from 48 % reported in cohorts from Cote d'Ivoire to > 95% in cohorts from South Africa. The ARV resistance rates are generally lower in Africa than in the Western world but again these numbers differ per country. The recommendations were that countries should be involved in facilitation, approval and distribution of HIV/AIDS medicines. The recommendations to financial partners (EDCTP or others) were to:

- Support countries in financing second-line ARV drugs and the management of side effects
- Assist countries in reinforcing diagnosis and treatment of opportunistic infections
- Assist countries in implementing the WHO 2006 recommendations
- Assist countries in reinforcing health care worker skills and training
- Support research, monitoring and evaluation

4.2 Presentations on organisations that could participate in HIV treatment trials in Africa

4.2.1 PENTA – Paediatric European Network for Treatment of AIDS

Dr Alexandra Campagnucci presented the aims and activities of PENTA. PENTA does not yet participate in Clinical Trials in Africa but is looking to expand its network to medium developed and developing countries. The main aims of PENTA are to:

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- Build a network of paediatric centres to undertake multicentre trials
- Address therapeutic questions specific to HIV infected children which cannot be answered by trials in adults
- Strengthen collaboration between paediatricians
- Improve knowledge and care of HIV infected children
- Expand the network to countries where ART therapy is being used in children
- Collaborate with other networks, next to continuation of the existing Network for “Medicine for children” (TEDDY)

PENTA works according to the European Clinical Trial Directive and has contributed to the development of new European regulations on Medicine for Children. PENTA has a unique expertise beyond running clinical trials. In Africa they have a capacity building ESPID/PENTA training programme for health care workers, which started in Cameroon in January 2007 and will start in Uganda later this year. Similar training programmes have been taught in Romania, London and Rome and part of the course is online available. PENTA's plans for the future are to start new projects on the evaluation of new ARV combinations, evaluation of immunotherapy (IL-2, vaccines), design of new strategies on toxicity reduction, evaluation of impact of metabolic disorders and adolescence.

4.2.2 ANECCA – African Network for the Care of Children Affected by HIV / AIDS

Dr. Nathan Tumwegigye presented the aims and activities of ANECCA. ANECCA is a network of persons involved and interested in promoting the paediatric HIV prevention, care and treatment in Africa. They do this through advocacy, technical assistance, training, research and networking in Africa. ANECCA wants to be a leading organisation in setting and guiding the agenda for paediatric HIV/AIDS prevention, care, treatment and support.

ANECCA gives technical assistance and support to strengthen training of providers in paediatric HIV prevention, care and treatment in Uganda, Kenya, Tanzania, Rwanda, Zambia, Malawi, Burundi, Zimbabwe, Namibia, DRC and W. African countries. Moreover, ANECCA is building sustainable local capacity and expertise for paediatric HIV treatment and care through Clinical Mentorship Programmes in Uganda, Kenya, Tanzania, Rwanda, Zimbabwe, Burundi, DRC and selected W. African countries.

ANECCA has developed a handbook on Paediatric AIDS in Africa available in English and French.

In order to generate evidence-based information for decision making in paediatric HIV/AIDS care ANECCA participates in collaborative research with:

- Paed ART: The KIDS-ART-LINC (KAL), which is a multi-centre, multi-country initiative of ANECCA and ISPED Bordeaux, which includes 25 paediatric HIV care and treatment centres in 16 African countries, with a total of 4513 children receiving ART (Dec 2006).
- Three paediatric HIV treatment centres in Northern Tanzania, Southern Malawi and Western Kenya for validation of 2006 WHO criteria.
- Pilot program for integration of paediatric HIV care with PMTCT/MCH and adult HIV care services at the Mbarara Regional Referral Hospital in Uganda with the aim to document best-practices.

ANECCA is still looking for more partners.

4.2.3 ARCAN – African Regional Capacity Building Network for HIV/AIDS prevention, treatment and care

Dr. Enoch Omonge presented the aims and activities of ARCAN. ARCAN is an African regional capacity building network for HIV/AIDS prevention, treatment and care. The current challenges for HIV treatment in Africa are to deal with: resistance to HAART, the high costs of care, drug toxicity and interactions, TB co-infections, the Immune Reconstitution Syndrome (IRIS), poor adherence of patients to treatment. Dr. Omonge presented data on the complications of HIV/TB co-infections and the ARCAN recommendations for when to start ART in HIV/TB co-infected patients.

4.3 Overview presented sites

Possible sites presented at the meeting		
Name of Institution	Target group	Country
French ANRS	Adults	Cameroon
	Adults	Cote d'Ivoire
	Adults	Senegal
	Adults	Burkina Faso
MRC	Children + adults	Zambia
	Children + adults	Zimbabwe
		Uganda (3 sites)
ANECCA	Children	Northern Tanzania
	Children	Western Malawi
	Children	Southern Kenya
	Children + adults	Mbarara, Uganda
		and others

4.3 Summary discussion on Sites in Africa

- In terms of networks for paediatrics the sites were well described. There are 26 available sites for paediatrics studies in Africa. What exists in terms of networks for adults is however, less clear, but it was agreed that if for a CT 14-15 sites would be needed this capacity would be available.
- It was generally agreed that the existing networks in Africa should be used, but that EDCTP should try to break the established ties between countries and aim for an "African network" setup combining resources of the MRC, ANRS etc. In order realise this the project should establish regional African networks, where less strong sites that could be strengthened during the trials by working with stronger sites. In this respect the Network of Excellence call and the DCCC work were explained.
- Clearly, however, some regions have been strengthened more than others in the past. Therefore it is important to keep identifying new sites to establish new networks, which include the areas where not yet many established sites are present.
- A discussion was held on qualifications of sites. It was mentioned that it takes at least 2 years to be internationally recognised and accredited as site based on the US model. It was acknowledged that a certification from the Western World is

unrealistic and may be unnecessary for the current needs. An African qualification system could accomplish the need for quality assurance in the development of sites on the continent.

- It was acknowledged that it is important that the Africans need to drive the collaborations.

5. EDCTP procedures

5.1 Overview EDCTP procedures

EDCTP can fund proposals through an open call or a brokering procedure. Both were explained to the audience. Furthermore information was given on the new tool Project Partners available on the EDCTP website, the EDCTP budget for HIV treatment and the expected results from the Stakeholders Meeting. More information can be found in the guidelines for Stakeholders Meetings (see Annex 2).

5.2 Summary discussion EDCTP funding procedure and timelines for initiating funding procedure

It was generally agreed that an open call would be the appropriate funding procedure for HIV treatment.

Recommended procedure: Open call

In terms of the call text the following suggestions were made:

- It was acknowledged that involvement of the pharmaceutical industry especially in the HIV/AIDS field is difficult in the early phases of clinical trials. Therefore a recommendation was made to focus on phase IV clinical trials.
- Projects should be funded that study second and third line treatment strategies.
- Since in comparison to the west the burden of HIV/AIDS among children in Africa is very high, special emphasis should be put on childhood studies.
- Strategic questions such as “when to start and when to switch” should be included in the call.
- It was acknowledged that many HIV/AIDS patients suffer from TB and other opportunistic infections, however with the limited budget available for HIV treatment (6,5 million euros) research on HIV/TB co-infections should not be a main priority.
- Regarding whether EDCTP should put all its money available on one call or divide among several calls, it was suggested to spend all available 6,5 million euros on one call.
- The audience was asked for an estimate on the costs of clinical trials. It was estimated that PK studies in 4 small groups of about 15 individuals would cost between 500,000 and 900,000 euros. A larger clinical trial involving 35-50 patients per arm with a duration of about 28 weeks was estimated to cost around 1,000,000 euros per trial. This amount is excluding any PK elements, capacity building etc.

Possible funding partners:

The table below lists the European countries that were represented at the meeting:

Pledged and potential contributions to topic		
Country	Type of support	Preferred subjects
Spain	Able to cofund projects if a	Critical issue is to provide

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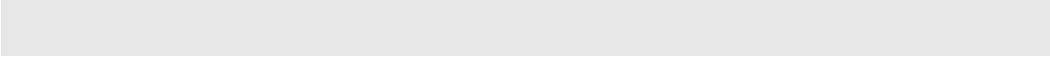
	Spanish team is part of the application. Spain therefore performs its own scientific and strategic assessment. In addition the core funding already allocated to EDCTP can be used.	knowledge to Africa. Preference for studies on second line treatment.
Ireland	Core funding already allocated to EDCTP can be used. EDCTP review procedure from scientific point of view is sufficient.	Would be happy to see EDCTP fund projects that include capacity building, based on the best science and affordable products with a focus on women and children.
United Kingdom	MRC funding should either go to Africa or to a UK partner of the project. MRC in general accepts principles of EDCTP review procedure. Another option is to fund projects through DFID, for which MRC is doing its own review procedure.	<ul style="list-style-type: none"> - Strategic questions - Second line drugs (when to switch what to switch to, how to monitor) - To include partnership with pharmaceutical company - Capacity development
Germany	Can strictly only fund German nationals	Accepts research strategy of EDCTP
Norway	Can fund only Norwegian research groups collaborating with partners in the south. Supports calls on competitive basis	
France	Funds can be shared with EDCTP, but cannot be transferred to EDCTP. For next 3 years 1 million per year available for HIV treatment in the south. Supports S-S networks, not N-N networks. French involvement is mandatory, use own review procedure.	
Belgium	Was not in position to make a pledge as it was represented by a scientific expert only.	

It was recognised that for EDCTP and the scientists it remains hard to deal with all cofunding requirements of the Member States.

6. Recommendations to EDCTP

The meeting agreed that the top two priorities for clinical trials were:

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- Support clinical trials using registered drugs with a focus on second line treatment. The questions when to switch from first to second line treatment, what products to switch too and how to monitor need to be addressed
 - Support of paediatric studies on fixed dose combinations in children possibly with a PK element
- 

7. Annexes

Annex 1: Member state and third party contribution to the stakeholder meeting

Estimate of all costs covered by hosting country	
Item	Amount
Travel	
Hotel	
Catering	575,00 Euros
Administration support	
Venue	
Other	
Sum	575,00 Euros

Signed by organising Member State:

Name

Date

Annex 2: EDCTP Guidelines for Stakeholder meetings

Introduction

This document aims to describe all aspects related to the aim, organisation and outcome of the EDCTP stakeholder meetings.

EDCTP aims to organise to 2 types of stakeholder meetings: 7 meetings will focus on disease specific topics and one meeting will concentrate on Nodes of Excellence. The disease-specific topics will have a focus on products in the pipeline. These topics are listed below:

- Malaria treatment and malaria in pregnancy (combined meeting)
- Malaria vaccines
- TB treatment
- TB vaccines
- HIV treatment
- HIV vaccines
- HIV microbicides

The Nodes of excellence meeting will focus on the integrated approach of EDCTP towards the establishment of regional nodes of excellence in sub-Saharan Africa with particular focus on reference laboratories and centres specialised in data management encompassing clinical trials design, conduct, and analysis skills, building on sites with existing capacities and competences in these areas.

These guidelines aim to describe the generic approach towards organising both types of meetings. All stakeholder meetings on disease related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP. The expected outcome, communication aspects, timelines and financial issues concerning stakeholder meetings will be clarified. In addition the role of the hosting member state, the organising committee including the independent chair as well as the expected list of participants are described.

To ensure transparency these guidelines are made public and the EDCTP Secretariat will ensure that the implementation will be carried out and documented correctly.

Aim and objectives of a stakeholder meeting

A stakeholder meeting is a one day meeting. It is the start of a process that leads towards EDCTP funding one or more projects through a call or brokering procedure.

The expected outcome of these meetings is:

1. To make recommendations to EDCTP for:
 - The development of cooperative projects and coordination of efforts
 - Priorities for EDCTP:
 - for disease specific topics EDCTP requires priorities in terms of product and sites whereas
 - for nodes of excellence EDCTP needs priorities in terms of sites, location as well as required skills and capacity
2. Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms. These will be followed up by the EDCTP secretariat.
3. Establishment of trust in the EDCTP approach with our stakeholders.

The meetings with a disease-specific topic will have the following objectives:

- Identify products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend priority in terms of product and sites
- Recommend if the funding procedure is a call or brokering or no-go
- Recommend EDCTP timelines concerning the initiation of funding for each topic area

The stakeholder meeting on Nodes of Excellence has similar priorities:

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- Identify potential sites
- Identify needs in terms of skills and capacity
- Recommend priorities in terms of needs and sites
- Recommend if the funding procedure is a call or brokering or no- go
- Recommend EDCTP timelines concerning the initiation of funding

Organisational aspects

All stakeholder meetings on disease-related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP.

All meetings will be organised by an Organising Committee that consists of:

- An independent expert to chair
- A representative of the hosting country. For the European Member States this is the European Networking Officer (ENO) representing the country while for the Nodes of Excellence meeting this role should be fulfilled by the relevant member of the Developing Country Coordinating Committee (DCCC),
- The Partnership Board (PB) and DCCC disease experts
- The Executive Director and Operations Manager from the EDCTP Secretariat

The independent chair will be identified by EDCTP Secretariat, PB and DCCC representatives of the organising committee before the date of the stakeholder meeting is set. The candidate will be approved by the GA in a written procedure. If the hosting country is identified before a chair is selected the representative of the hosting country will also be involved in selecting the chair. The Terms of reference for the Independent chair are the following:

To work with the EDCTP stakeholders' meeting planning group to ensure that the meeting is planned and implemented transparently avoiding or declaring any conflict of interest to give an optimal, independent and objective advice to the EDCTP. This, via the EDCTP Secretariat should take into account the following:

1. The presence of appropriate representation of all significant bodies including industry, private-public partnerships and other stakeholders that are relevant to the topic; ensuring that the representation at the meeting is sufficiently senior to contribute with authority
2. There are appropriate and effective arrangements for conducting the meeting including drafting and approving of the agenda; noting of the attendance; ensuring of adequate participation and deliberation of all the relevant issues
3. Provision in an agreed timescale of a good quality report of the meeting.

Travel and hotels are arranged in close collaboration between the hosting country and the EDCTP Secretariat and the hosting country is expected to play an active role in this. The hosting country should organise location, catering and administrative support as well as assist delegates with their visa requirements. In addition the hosting country is responsible for sending out the invitations to participants. The final list of participants to be invited will be provided by the EDCTP Secretariat in collaboration with the Organising Committee.

Participants

It is a requirement that the following parties are represented at the stakeholder meeting:

- Funders both from the European Member States and if applicable third parties. Each European Member State will be asked to send one representative. It is up to the individual country to accept this invitation or not
- Product developers, Public Private Partnerships and/or industry (disease specific topics only)
- Representatives of African sites that have the capacity to carry out phase II or III trials
- Experts in the field. Each European Member State may bring one expert of their own choosing

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- Independent experts if applicable.

Most participants will be identified by the Organising Committee with the exception of the representatives of the European Member States. Each European Member State is free to send one expert in the field and one representative of their funding body of their own choosing.

It is normally expected that a stakeholder meeting will have no more than around 40 participants.

Invitations to the participants need to go out at least 6 weeks in advance.

Agenda

The agenda for the stakeholder meeting is set by the Organising Committee using the format developed by the EDCTP Secretariat. The generic format for the meetings on disease specific topics is shown below.

EDCTP Stakeholder Meeting

Topic
location, date 2007
Address
Contact

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	
1.0 Welcome by host	host	
2.0 Approval of the Agenda	All	
3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline: relevant stakeholder (more added if required) More added if required		
Coffee break	All	
4.0 Discussion on products and science	All	
5.0 Sites in Africa 5.1 Relevant stakeholder (more added if required) 5.3 DCCC		
Lunch	All	
6.0 Discussion on sites	all	
7.0 EDCTP procedures	SEC	
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	
9.0 Summary of recommendation	Chair	

Communication

Because EDCTP stakeholder meetings should demonstrate transparency and independence it is important that the meetings are widely advertised and that the hosting country does not have a perceived conflict of interest with the topic. EDCTP will however, not publish a call for participants. The advertisements for the stakeholder meetings will focus on announcement of topics, locations, aims and dates. They should list a contact address and encourage those that would like more information to make contact. If someone contacts EDCTP with a wish to participate, this request will be passed on to the Organising Committee who will make a decision.

Advertising of the stakeholder meetings will be through the following means:

- Internet:
 - EDCTP website
 - Requesting constituency members to publish at their websites
 - Other relevant websites
- Paper advertisement:
 - Publishing of adverts in Lancet as soon as all the dates are set
- Ask EDCTP constituencies to communicate to appropriate parties
- If the opportunity arises mention of EDCTP stakeholder meetings in presentations or meetings

Timelines

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The dates for the various stakeholder meetings will be set as soon as the independent chair and hosting country have been identified and once the chair agrees to the Terms of Reference. It is expected that the stakeholder meetings for TB vaccines, malaria vaccines, HIV vaccines and HIV treatment will take place during the first quarter of 2007. The stakeholder meetings for Nodes of Excellence, malaria treatment/pregnancy, TB treatment and HIV microbicides are scheduled for the second quarter of 2007.

Financial issues

If the stakeholder meeting is hosted by a European country, it is expected that this country will at least as a minimum cover the costs for use of the location, catering during the meeting, administrative support and any other local expenses. If the hosting country is African these costs need to be discussed with the EDCTP Finance Manager. EDCTP will normally pay for travel and hotel for external participants as well as for PB and DCCC members. EDCTP expects that the European Member states will at least pay for travel and hotel of the participants they delegate. EDCTP will pay for travel and hotel of European MS participants and experts only if the European Member State is unable to do so.

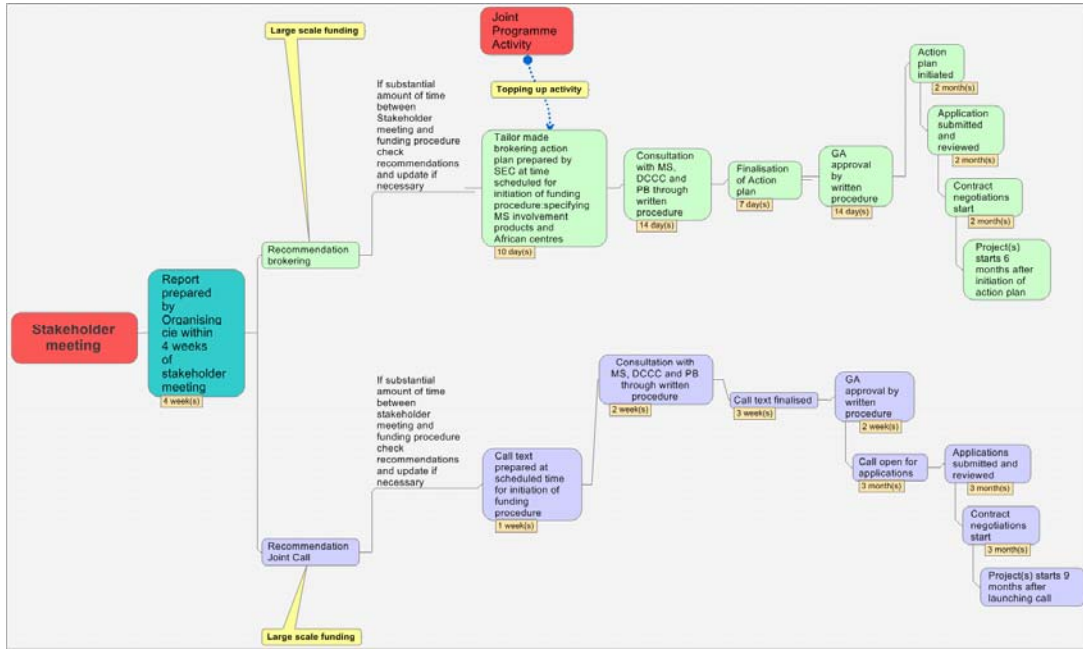
Outcome/follow up

The organising committee will produce a report of the meeting within 4 weeks. The report will be presented to EDCTP. EDCTP will initiate its funding procedures at the appropriate time after considering the report. The timing for launching calls or brokering initiatives can range from 2007-2009 depending on the on the availability of products and sites. A final list of expected dates for initiation of funding procedures will be prepared after all stakeholder meetings have taken place. The diagram below summarises both funding procedures. More information on the EDCTP funding procedures can be found at the website.

A summary of both procedures is described below:

- *Call for proposals*
A call text is drafted based on the recommendations that came out of the stakeholder meeting. After consultation of the various EDCTP constituencies and approval of the General Assembly the call will be published. An EDCTP call is normally open for applications for a period of 3 months. The applications are then checked against the eligibility criteria as defined in the call text and eligible applications will be reviewed by at least 2 external experts as well as the EDCTP Scientific Review Committee (SRC). The SRC ranks the applications and makes a recommendation for funding. This recommendation is examined by the PB which ensures the quality of the review procedure and also assess if the proposal is in line with the EDCTP strategy. The PB make the final recommendation for funding to the General Assembly who approve the application.
- *Brokering*
A brokering action plan is prepared by the EDCTP Secretariat and requires to be approved by the General Assembly after consultation with the EDCTP constituencies. The action plan will be initiated resulting in an application for funding. This application is checked for eligibility as described in the brokering action plan and reviewed by at least two external experts as well as the relevant EDCTP SRC. The SRC make a recommendation for funding or rejection which is examined by the PB which examines both the procedure as well as the alignment of the project with the EDCTP strategy. Upon recommendation of the PB the GA make the decision to fund the project or not.

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Annex 3: Instructions for presentations

Expected outcome of the meeting

The expected outcome of the EDCTP stakeholder meetings is to make recommendations to EDCTP for:

- The development of cooperative projects and coordination of efforts
- Priorities for EDCTP in terms of product and sites
- Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms.
- Establishment of trust in the EDCTP approach with our stakeholders

The stakeholder meeting is considered the start of a process that leads towards EDCTP funding of one or more projects through an open call or brokering.

Audience

The audience will be a mixture of experts in the field and people who represent funding agencies and may not have a scientific/medical background. Therefore we would like to suggest that your presentation should be aimed at a general audience.

Expected contents of your presentation

Given the expected outcome of the meeting and the composition of the audience EDCTP would like to provide you some points regarding the expected contents of your presentation.

If you talk about science and products

- A short introduction on the organisation you are representing
- Without going into too much scientific details basic information about the products in the pipeline:
 - Basic principles of the product
 - Status with respect to clinical testing: what has been done/what is ongoing and what is planned/needed
 - Availability of the product
 - Restrictions with respect to the use of the product: is it only available for persons associated with your organisation/is it for sale?

In addition to the presentation could you provide a short summary document on each product that should enable the participants to the meeting to assess its scientific validity and potential.

If you talk about sites in Africa

- A short introduction on the organisation you are representing
- Basic information about the sites you are representing:
 - Capacity and trial experience
 - Commitment to other trials/availability to do the trial
 - Local malaria situation

Duration of your presentation

The time available per presentation is limited to 15 minutes. The presentations will be followed by an initial discussion of 1 hour.

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Annex 4: Agenda

HIV Treatment

Madrid, 24th May 2007

Auditorio CNIO

Instituto de Salud Carlos III

Sinesio Delgado 6

Madrid 28029

10:00-16:30

Aim of the meeting:

- Identify and prioritise potential products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend if the funding procedure of EDCTP will be an open call, brokering or whether EDCTP should fund this topic at all
- Recommend EDCTP 's timeline concerning the initiation of funding for this topic

Agenda items	By	Timelines
1.0 Welcome	Charles Mgone, Carmen Audera Chair Prof Robert Murphy	10:00-10:15
2.0 Approval of the Agenda	All	10:15: 10:20
3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline pediatric trials: PENTA	José María Miró Alex Compagnucci	10:20-10:35 10:35-10:50
<i>Coffee break</i>	All	10:50-11:10
4.0 Discussion on products and science	<i>All</i>	<i>11:10-12:00</i>
5.0 Sites in Africa 5.1 Needs in field of HIV treatment 5.2 ANECCA 5.3 ARCAN	Souleymane Mboup Nathan Tumwesigye Dr. Enock Omonge	12:00-12:15 12:15-12:30 12:30-12:45
6.0 Discussion on sites	all	12:45-13:30
<i>Lunch</i>	<i>All</i>	<i>13:30-14:30</i>
7.0 Concluding remarks on sites	Chair	14:30-14:45
8.0 EDCTP procedures	Cynthia Naus	14:45-15:00

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9.0 Member States commitment	Member State representatives	15:00: 15:30
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	15:30-16:15
9.0 Summary of recommendation	Chair	16:15: 16:30

Annex 5: List of participants

**HIV Treatment Stakeholder Meeting
Wednesday 24 May 2007, Madrid, Spain**

<p>Carmen Audera Instituto de Salud Carlos III Sinesio Delgado 6 E-28029 Madrid Spain Phone: 0034 9 1822 2449 Fax: 0034 9 1387 7830 E-mail: caudera@isciii.es</p>	<p>Rafael de Andrés Medina Instituto de Salud Carlos III Sinesio Delgado 6 E-28029 Madrid Spain Phone: 0034 918222508 E-mail: ram@isciii.es</p>
<p>Brigitte Bazin Responsable du Service “ Recherches dans les pays en développement” Agence Nationale de Recherche sur le SIDA et les Hépatites virales (ANRS) 101 rue de Tolbiac 75013 Paris France Phone: +33 153 94 60 46 Fax: +33 153 94 60 01 E-mail: brigitte.bazin@anrs.fr</p>	<p>Detlef Boecking Federal Ministry for Education and Research, "Health Research" Heinrich Konen Str. 1 53227 Bonn Germany Phone: +49 228 3821 118 Fax: +49 228 3821 257 E-mail: Detlef.Boecking@dlr.de</p>
<p>Charles Boucher European Cohort Coordinating Network on HIV Drug Resistance Lucas Bolwerk 14 3512 EH Utrecht The Netherlands Phone: +31 30 250 6526 E-mail: c.boucher@umcutrecht.nl</p>	<p>Norbert Brockmeyer Ruhr Universität Bochum University Hospital Bochum St Joseph Gudrunstr. 56 D-44791 Bochum Germany Phone: +49 234 509 3474 Fax: +49 234 509 3472 E-mail: n.brockmeyer@derma.de</p>
<p>Robert Colebunders Prince Leopold Institute of Tropical Medicine</p>	<p>David Coles EDCTP</p>

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<p>Nationale Straat 155 B-2000 Antwerp Belgium Phone: + 32 32476426 Fax: + 32 32476432 E-mail: bcoleb@itg.be</p>	<p>P.O. Box 93015 2509 AA The Hague The Netherlands Phone: +31 70 344 0885 Fax: +31 70 344 0899 E-mail: coles@edctp.org</p>
<p>Alejandra Compagnucci Paediatric European Network for Treatment of AIDS (PENTA) 10 Allée de la Vigne 92350 le Plessis Robinson France Phone: + 33 620 98 4068 E-mail: a.compagnucci@vjf.inserm.fr</p>	<p>Diana Gibb Clinical Trial Unit. MRC UK 222 Euston Road London NW1 2DA UK Phone: +44 207 670 4709 Fax: +44 207 670 4685 E-mail: dmg@ctu.mrc.ac.uk</p>
<p>Luis Guerra Instituto de Salud Carlos III Sinesio Delgado 6 E-28029 Madrid Spain Phone: 0034 9 18222208 Fax: 0034 9 1387 7830 E-mail: luisguerra@isciii.es</p>	<p>Marianna Karras EDCTP P.O. Box 93015 2509 AA The Hague The Netherlands Phone: +31 70 344 0844 Fax: +31 70 344 0899 E-mail: karras@edctp.org</p>
<p>Kårstein Måseide The Research Council of Norway P.O. Box 2700, St. Hanshaugen N-0131 Oslo Norway Phone: 0047 2203 7457 Fax: 0047 2203 7362 E-mail: kmaa@rcn.no</p>	<p>Souleymane Mboup Cheikh Anta DIOP University, Faculty of Medicine, Bacteriology Virology Laboratory 30 Avenue Pasteur CHU Aristide Le Dantec Dakar Senegal Phone: 00221 8216420 / 8225919 Fax: 00221 821 64 42 E-mail: virus@sentoo.sn; mboup@eci.harvard.edu</p>

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<p>Charles Mgone EDCTP P.O. Box 93015 2509 AA The Hague The Netherlands Phone: 0031 70 344 0880 Fax: 0031 70 344 0899 E-mail: mgone@edctp.org</p>	<p>José M. Miró Hospital Clinic Universitari Helios-Villarroel Building - Desk no. 26 Villarroel, 170 08036 Barcelona Spain Phone: 34-93-2275400 (Ext. No. 2765) Fax: 34-93-4514438/5424 Email-1 jmmiro@ub.edu (work) Email-2 miro97@fundsoriano.es (home) http://www.hospitalclinic.org</p>
<p>Laura Mohedano Macías Instituto de Salud Carlos III Oficina de Proyectos Europeos C/ Sinesio Delgado, 6 28029 Madrid (Spain) Tel.: + 34 91 822 23 77 email: lmohedano@isciii.es</p>	<p>Robert Murphy Northwestern University 676 N. Saint Clair Street, Suite 200 Chicago, IL 60611 USA Phone: +1 312 695 4994 Fax: +1 312 695 5088 E-mail: r-murphy@northwestern.edu</p>
<p>Cynthia Naus EDCTP P.O. Box 93015 2509 AA The Hague The Netherlands Phone: 0031 70 344 0892 Fax: 0031 70 344 0899 E-mail: naus@edctp.org</p>	<p>Peter Ndumbe EDCTP - DCCC University of Buea Faculty of Medicine PO Box 63 Molyoko, Buea Cameroon Phone: +237-332 2134 Fax: +237-231 27 33 E-mail: pndumbe@yahoo.com</p>
<p>Enock Omonge African Regional Capacity Building Network for HIV/AIDS Prevention, Treatment & Care (ARCAN)</p>	<p>Marjolein Robijn EDCTP P.O.Box 93015 2509 AA The Hague</p>

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<p>PO Box 28820 Nairobi 00200 Kenya Phone: +254 721 562 033 E-mail: omongedr@yahoo.com</p>	<p>The Netherlands Phone: +31 70 344 08 93 Fax: +31 70 344 08 99 E-mail: robijn@edctp.org</p>
<p>Manuel Romaris Scientific Officer for HIV/AIDS Research European Commission CDMA 03/35 Rue du Champ de Mars/Marsveldstraat 21 1049 Brussels (Belgium) Phone: 32 2 299 87 33 Fax: 32 2 299 45 61 E-mail: manuel.romaris@cec.eu.int</p>	<p>Mairin Ryan St James Hospital National Centre for Pharmacoeconomics James´ Street 8 Dublin Ireland Phone: +353 1 41 62523 Fax: +353 1 47 30596 E-mail: mairin.ryan@ireland.com</p>
<p>Fernand Sauer European Commission 65, rue des Bollandites 1040 Brussels E-mail: fernandsauer@hotmail.com</p>	<p>Nathan Tumwesigye ANECCA (anecca@rcqhc.org) Regional Centre for Quality of Health Care Makerere University Institute of Public Health P.O. Box 29140, Kampala – Uganda Phone: 256 41 530 888 Fax. 256 41 530 876 E-mail: ntumwesigye@rcqhc.org ntumwesigye@gmail.com</p>
<p>Lynn Zijenah EDCTP – DCCC University of Zimbabwe Immunology Department, Medical School P O Box A178 Avondale, Harare Zimbabwe Phone: +263 4 791631 Fax: +263-4-724912 E-mail: sodai@mweb.co.zw</p>	

Annex 6: Discussion paper

Recommendations of GESIDA/Spanish AIDS Plan on antiretroviral therapy in adults infected by the human immunodeficiency virus (Updated January 2007)

Expert Committee of GESIDA and the National AIDS Plan

OBJECTIVE. This consensus document is an update of antiretroviral therapy (ART) recommendations for adult patients infected with the human immunodeficiency virus (HIV-1).

METHODS. To formulate these recommendations, a panel composed of members of the *Grupo de Estudio de Sida* (GESIDA; AIDS Study Group) and the *Plan Nacional sobre el Sida* (PNS; Spanish AIDS Plan) reviewed the advances in the current understanding of the pathophysiology of HIV, the safety and efficacy findings from clinical trials, and the results from cohort and pharmacokinetic studies published in biomedical journals or presented at scientific meetings over the last years. Three levels of evidence were defined according to the source of the data: randomized studies (level A), cohort or case-control studies (level B), and expert opinion (level C). The decision to recommend, consider or not recommend ART was established in each situation.

RESULTS. Currently, the treatment of choice for chronic HIV infection is the combination of three drugs of two different classes, including 2 nucleosides or nucleotide analogs (NA) plus 1 non-nucleoside (NN) or 1 boosted protease inhibitor (PI/r). Initiation of ART is recommended in patients with symptomatic HIV infection. In asymptomatic patients, initiation of ART is recommended on the basis of CD4+ lymphocyte counts and plasma viral load, as follows: 1) therapy should be started in patients with CD4+ counts of < 200 cells/ μ L; 2) therapy should be started in most patients with CD4+ counts of 200-350 cells/ μ L, although it can be delayed when CD4+ count persists at around 350 cells/ μ L and viral load

is low, and 3) initiation of therapy can be delayed in patients with CD4+ counts of > 350 cells/ μ L. The initial objective of ART is to achieve an undetectable viral load. Adherence to therapy plays an essential role in maintaining the antiviral response. Therapeutic options are limited with the development of cross resistance and ART failure. Genotype studies are useful in these cases. More information regarding the studies analyzed and the panel recommendations for adherence, toxicity, treatment during pregnancy, patients with hepatitis B or C virus co-infection, and post-exposure prophylaxis can be accessed at www.gesida.seimc.org.

CONCLUSIONS. CD4+ lymphocyte count is the most important reference factor for initiating ART in asymptomatic patients. The large number of available drugs, the increased sensitivity of tests to monitor viral load, and the ability to determine viral resistance is leading to a more individualized approach to therapy.

Key words: Antiretroviral treatment. AIDS. HIV infection. GESIDA. PNS (Plan Nacional sobre el Sida). Antiretroviral resistance. Guidelines.

Recomendaciones de GESIDA/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (actualización enero de 2007)

OBJETIVO. Efectuar una actualización de las recomendaciones sobre el tratamiento antirretroviral (TARV) de los adultos infectados por el VIH-1.

MÉTODOS. Estas recomendaciones se han consensuado por un panel del Grupo de Estudio de Sida y del Plan Nacional sobre el Sida. Se han revisado los avances en la fisiopatología del VIH-1, los resultados de eficacia y seguridad de ensayos clínicos, estudios de cohortes

Correspondence: Dr. J. López Aldeguer.
Unidad Enfermedades Infecciosas. Hospital La Fe.
Avda. Campanar, 21. 46009 Valencia. España.
E-mail: lopez_jos@gva.es

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y de farmacocinética, publicados en revistas biomédicas o presentados en congresos en los últimos años. Se han definido tres niveles de evidencia según la procedencia de los datos: estudios aleatorizados (nivel A), de cohortes o de caso-control (nivel B), u opinión de expertos (nivel C). En cada una de las situaciones se ha establecido recomendar, considerar o no recomendar el TARV.

RESULTADOS. Actualmente, el TARV con combinaciones de tres fármacos constituye el tratamiento de inicio de elección de la infección crónica por el VIH-1. Estas pautas deben incluir 2 análogos de nucleósido o nucleótido (AN)+ 1 no análogo (NN) o 2 AN+ 1 inhibidor de la proteasa (IP) potenciado con ritonavir. En los pacientes con infección por VIH-1 sintomática se recomienda iniciar el TARV. En los pacientes asintomáticos el inicio de TARV se basará en la cifra de linfocitos CD4+ / μ l y en la carga viral plasmática (CVP): 1) en pacientes con linfocitos CD4+ < 200 céls./ μ l se recomienda iniciar el TARV; 2) en pacientes con linfocitos CD4+ entre 200 y 350 céls./ μ l en la mayoría de las ocasiones se debe recomendar el tratamiento, si bien se podría diferir cuando la cifra de linfocitos CD4+ se mantiene próxima a 350 céls./ μ l y la CVP es baja; 3) en los pacientes con linfocitos CD4+ > 350 céls./ μ l se puede diferir el inicio del TARV.

El objetivo del TARV es lograr una carga viral plasmática indetectable. Las opciones terapéuticas en los fracasos del TARV se ven limitadas por la aparición de resistencias cruzadas. Los estudios genotípicos en estos casos son de utilidad. Se puede encontrar más información sobre los estudios analizados, las recomendaciones del panel sobre adherencia, toxicidad, tratamiento de la embarazada, pacientes coinfectados por VHB o VHC o sobre la profilaxis postexposición en la página web www.gesida.seimc.org.

CONCLUSIONES. La cifra de linfocitos CD4+ es el factor de referencia más importante para iniciar el TARV en pacientes asintomáticos. Por otra parte, el número considerable de fármacos disponibles, los métodos más sensibles de monitorización de la CVP y la posibilidad de determinar las resistencias hacen que las estrategias terapéuticas deban ser cada vez más, mucho más individualizadas.

Palabras clave: Tratamiento antirretroviral. Sida. Infección por VIH. GESIDA. PNS (Plan Nacional sobre el Sida). Resistencia a antirretrovirales. Guía.

Introduction

Since highly active antiretroviral therapy became part of clinical practice in 1996, the number of antiretroviral drugs available and their possible combinations have continued to grow. At the same time, research in the field of antiretroviral therapy (ART) has taught us the best way of using these combinations, although clinical decisions on the best antiretroviral therapy should be based on expert recommendations in the absence of data of better methodological quality. This situation has led different interna-

tional scientific societies and institutions to prepare and update their own recommendations on the use of antiretroviral drugs¹⁻³.

In Spain, the Plan Nacional sobre el Sida (PNS: Spanish AIDS Plan) and the Grupo de Estudio de Sida (GESIDA: AIDS Study Group) of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC: Spanish Society for Infectious Diseases and Clinical Microbiology) have been working together closely for several years to obtain a consensus among the health-care professionals who treat HIV-1-infected individuals, and provide updated and validated recommendations to physicians with less experience in the treatment of this infection. Therefore, they regularly publish documents that update recommendations on antiretroviral therapy in HIV-1-infected adults. These documents are drawn up by an expert committee selected by both institutions.

The present document replaces that published in 2004⁴ and its 2005 update published on the web pages of GESIDA and the PNS.

These guidelines have been updated by reviewing the most relevant scientific data taken from scientific journals or communications at scientific meetings.

This document aims to answer questions relating to the indication to initiate or modify ART, and the selection of the most suitable combinations. The committee has also performed an in-depth review of other aspects associated with antiretroviral therapy, such as adherence, toxicity, drug-drug interactions, or special situations (coinfection by the hepatitis virus, therapy in pregnant women, or post-exposure prophylaxis). However, for editorial reasons, these special areas are not dealt with in the present article although they are available in an extended version of the document available on the web pages of GESIDA (www.gesida.seimc.org) and the PNS (<http://www.msc.es>). The extended version also provides a more exhaustive review of the studies and data on which the recommendations are based. The characteristics of the different antiretrovirals, their possible pharmacokinetic and adverse effects, and the cost of the recommended regimens are presented in a table.

Data on antiretroviral therapy change constantly; therefore, readers should regularly consult other sources of information.

Evaluation of the degree of scientific evidence

As in previous editions of this document, the levels of recommendation used in the first edition of the Recommendations of the Advisory Committee of the National AIDS Plan, which are based on the source of the data: level A: randomized and controlled studies, level B: cohort or case-control studies and level C: descriptive studies or expert opinion.

General principles

The state of the art in HIV-1 infection allows us to establish the following principles:

1. ART of choice is based on combinations of three drugs, as this delays clinical progression, reduces hospi-

tal admissions and infection-related costs, and significantly increases survival⁵⁻¹⁴.

2. Adherence to ART plays a crucial role in virological response and its duration¹⁵.

3. Clinical symptoms, CD4+ lymphocyte count and HIV-1 RNA viral load (VL) are the basis for taking therapeutic decisions in different clinical situations and for monitoring the effectiveness of ART^{1,3,4,16}.

4. Treatment aims to reduce VL to below the limits of detection set by commercially available methods, wherever possible by ultrasensitive methods (< 20 to < 50 copies/mL), and for as long as possible^{1,3,4,17}.

5. Resistance is an inevitable phenomenon when HIV-1 is exposed to the selective pressure of one or more drugs that do not manage to suppress viral replication.

6. In patients with advanced immunodepression, restoration of the immune system in both quantitative terms (absolute CD4+ lymphocyte figure) and qualitative terms (quality of the immune function) is possible with current ART regimens^{16,18}.

7. As of January 2007, we have at our disposal 20 drugs belonging to four families which, together with other tools for guiding ART, make possible therapeutic strategies that are much more dynamic and individualized.

8. Medium-term and long-term toxicity of antiretroviral drugs is a limiting factor that forces us to seek out new options capable of limiting or eliminating side effects while maintaining antiviral potency¹⁹.

9. There are probably several ART regimens that are similar in terms of antiretroviral potency^{1,3,4,20}, and choice will depend on patient and physician preference, secondary effects, tolerance and adherence, previous therapy, possible cross-resistance, potential pharmacological interactions, and cost and availability of antiretroviral drugs.

10. The increasing complexity of ART means that patients must be attended by specialized staff with sufficient knowledge and means²¹.

11. Prevention of HIV-1 infection is a basic aspect of HIV-1 infection that must never be forgotten in clinical practice.

Parameters for guiding antiretroviral therapy

The patient's clinical situation (presence or absence of opportunistic events), CD4+ lymphocyte count, and VL are the parameters used to take decisions on initiating and modifying ART and to monitor its efficacy.

Clinical manifestations

Most opportunistic events occur in immunodepressed patients whose criteria indicate that ART should be initiated. The onset of an opportunistic disease in a patient on ART should be considered as a therapeutic failure.

Nevertheless, the onset of an opportunistic infection during the first 3-6 months of ART in patients with advanced immunodepression and a suitable virological response (immune reconstitution) cannot be considered a therapeutic failure^{22,23}.

RECOMMENDATIONS

- Clinical progress must be monitored at all visits, since it could be a reason for switching therapy (level C).

- In the care setting, a clinical check-up should be made 4 weeks after initiating ART and then every 3-4 months. In patients with advanced immunodepression, a more frequent follow-up should be performed, at least initially, whereas in stable patients this period can be extended (level C). Biological check-ups (VL, CD4+ lymphocytes) should be carried out with the same frequency as the clinical check-ups (every 3 or 4 months). It is very important to evaluate the adherence, toxicity, and potential pharmacokinetic interactions of ART at all check-ups.

CD4+ lymphocytes

One objective of ART is immune restoration, and the most practical way to evaluate it is by measuring the increase in the number of CD4 lymphocytes that can be observed during the first weeks after initiating ART^{16,18,24,25}. The proliferative response to memory antigens and mitogens is restored and this allows prophylaxis of opportunistic infections to be suspended²⁴⁻²⁶.

The increase in the number of CD4 lymphocytes is slow but constant over time. There are no data that enable us to provide a definition of adequate immune response. In general, cell kinetics studies show that during the first year there should be an increase of at least 50-100 CD4 lymphocytes/ μ L²⁷. Immune failure is usually preceded by virological failure and modifications to ART usually depend on VL. Discordance between the immune response and the virological response to ART can sometimes be observed.

RECOMMENDATIONS

- The number of CD4 lymphocytes is the most important parameter for deciding when to initiate ART. Therefore, it should be measured at the first visit so that decisions on when to initiate ART can be made (level B). On the contrary, the number of CD4 lymphocytes is a less important criterion than VL when deciding on modifications to therapy.

- In asymptomatic patients, the number of CD4 lymphocytes should be measured every 3 or 4 months; this interval can be extended if the patient is stable. The variability of the technique (\pm 20%) means that the number of CD4 lymphocytes must always be repeated before taking any decisions concerning therapy²⁸⁻³⁰.

HIV-1 viral load in plasma

The objective of ART is to suppress viral replication as quickly and for as long as possible. VL falls quickly (1-2 log₁₀/mL) after initiating ART and the nadir reached at 4-8 weeks correlates with the duration of the response³¹⁻³³. In naïve patients, VL levels that are undetectable using conventional techniques (< 200/50 copies/mL) are usually reached after 3-8 weeks of ART³⁴.

Some patients, especially those who start with a high VL, can take more than 24 weeks to reach levels below 20-50 copies/mL³⁵.

It is important to reach a VL below 20-50 copies/mL, since it has been shown that, although the virus replicates in lymphatic tissue, if VL is below this level, resistance mutations are not selected^{36,37}. Furthermore, the duration of the virological response at 18-24 months is much greater for those individuals who reach a VL of < 20 copies/mL than for those who maintain a VL of between 20 and 500 copies/mL³². Although some studies show that there is a greater risk of failure in patients who experience frequent transitory rebounds in VL (blips)³⁸, most do not show a great incidence of virological failure in patients with a complete virological response³⁹⁻⁴². In any case, a VL above 50 copies/mL in two successive determinations must be considered a virological failure.

On the basis of viral kinetics in patients with ART, the criteria for virological response and failure are as follows:

Virological response: VL < 20/50 copies/mL at 16-24 weeks. These patients have a virological response at 1 month (decrease > 1 log₁₀/mL), and at 3-4 months they have an undetectable VL using conventional techniques.

Virological failure: any of the following situations define virological failure: *a*) detectable VL at 24 weeks after initiating ART, or *b*) if after reaching an undetectable VL (< 50 copies/mL), it becomes detectable in two successive determinations.

RECOMMENDATIONS

- VL is the main parameter for evaluating the efficacy of ART, for defining its failure and, therefore, for taking decisions about modifications to therapy (see "Experienced patients"). At present, VL is recognized as a secondary criterion for the initiation of ART, complementary to the number of CD4 lymphocytes. Follow-up of the efficacy of ART should use, whenever possible, an ultrasensitive method of measuring VL (level B). The same technique should be used habitually. VL should always be confirmed with a second determination before making any decisions about therapy (level B).

- As far as frequency of tests is concerned, it is advisable to measure VL four weeks after initiating ART in order to verify whether there is a virological response and as an indirect measure of adherence. Levels should be measured every 3-4 months afterwards, although this interval can be extended in stable patients. We must bear in mind that, if VL is measured after an intercurrent viral process or after vaccination (e.g. anti-influenza or hepatitis B vaccine), there may be transitory rebounds in VL. In this case, a new analysis is recommended after a few weeks⁴³.

Resistance of HIV-1 to antiretroviral drugs

The appearance of viral strains with resistance variants can be detected using genotypic or phenotypic techniques⁴⁴. Genotypic techniques detect specific changes in the genomes of the enzymes that are targeted by the action of drugs (reverse transcriptase and protease), whereas phenotypic techniques determine the response to most of the viral population at increasing concentrations of the different drugs. Both techniques have limitations: on

the one hand, the resistant variants may not be detected by most genotypic and phenotypic tests until they make up 20% of the viral population and, on the other, technical limitations make it difficult to obtain reliable results when VL is below 1,000 copies/mL of HIV-1 RNA⁴⁴. Finally, resistance tests should be performed during ART⁴⁵ and not after interrupting it, since the resistant viral population will be replaced by a sensitive population a few weeks after the drugs are withdrawn. The results of resistance tests should be interpreted bearing in mind previous ART and resistance studies, as well as adherence.

The literature contains numerous studies from the developed world that have analyzed the frequency of primary resistance in patients with acute and chronic HIV-1 infection before receiving ART. We now know that most mutations can be detected over many years and that, as has recently been confirmed in the U.S. and in Europe⁴⁶⁻⁴⁸, the prevalence of primary resistance has increased considerably, in some cases to more than 10%. Nevertheless, in order to know the possible implications for therapy in a specific country, it is very important to analyze local data. Several studies have been carried out in both situations in Spain^{49,50}. One multicenter study of recently infected patients found a prevalence of 14% of strains containing resistance mutations⁵¹ and the researchers verified its relationship with the prevalence of patients with a detectable VL⁵². One study from the U.S. used a similar model to determine the clinical benefit and cost-efficacy relationship of genotypic resistance testing on all chronically infected naïve patients using a simulated model of HIV-1 (*The Cost-Effectiveness of Preventing AIDS Complications model*), based on the parameters of the natural history of the infection obtained from the MACS cohort. The authors conclude that the genotypic study is cost-effective in these patients and should therefore form part of their health care^{53,54}.

In pregnant women, there is a clear relationship between VL and the risk of vertical transmission⁵⁵. This risk has also been observed to be 5 times greater if there are zidovudine (ZDV)-resistant strains, and this factor is independent of VL⁵⁶.

RECOMMENDATIONS

- Resistance studies are helpful, as they allow drugs to be used better⁴⁴ (level A). There is also a public health benefit for the community, since better use of ART will probably reduce the appearance potentially transmissible resistance (level C).

TABLE 1. Indications for resistance testing in clinical practice*

A. Naïve patients
Pregnant women
Acute HIV infection
Post-exposure prophylaxis (source case)
Patients about to start ART (if no previous study is available)
B. Experienced patients
After any failure

*All patients should undergo genotypic resistance testing before initiating antiretroviral therapy. This could be included as part of the initial screening.

ART: antiretroviral therapy; HIV: human immunodeficiency virus.

- At present, genotypic testing to detect resistance is indicated in health-care practice⁵⁷ in the situations set out in table 1.

Acute HIV-1 infection

HIV-1 primary infection is symptomatic in more than half of all cases, although it could go unnoticed, as its symptoms are similar to those of common virosis, and this usually delays diagnosis⁵⁷⁻⁶¹. Therefore, this should be suspected in all seronegative patients with HIV-1 risk practices and compatible symptoms. As there are still no antibodies at this stage (window period), VL should be determined or, if this is not possible, antigen p24 should be determined. The sensitivity and specificity of VL are 100% and 97% respectively⁶²; the few false positives by this technique usually have a low VL (< 10,000 copies/mL). The sensitivity and specificity of p24 antigenemia in plasma are 89% and 100%, respectively⁶². In general, these patients' VL is very high, often more than 6 log₁₀/mL. Clinical manifestations usually appear about 2 weeks after infection and with current ELISA testing, seroconversion can be detected 1-2 weeks later⁶³. By contrast, HIV-1 RNA can be detected in plasma the week before the onset of symptoms. In all these cases, HIV-1 infection should be confirmed using *Western blot*. In the initial phase, *Western blot* can be negative or show only a few bands (indeterminate); therefore, it should be repeated a few weeks later. The clinical picture of primary infection is generally similar to that of mononucleosis or viral meningoencephalitis⁶¹. The clinical manifestations are more numerous and severe the greater the VL. Fever, myalgia, night sweats, and arthralgia are common in patients with primary infection¹⁴³. Acute infection (diagnosed before seroconversion) should not be confused with recent infection (less than six months' duration)⁶¹.

At present, initiating ART during acute infection is somewhat controversial⁶⁴, given that its possible benefits remain uncertain. This is due to the fact that clinical information is limited to small series, generally with no control group, and that no clinical trial has yet shown a medium-to-long-term clinical benefit in reducing progression to AIDS or death, compared with initiating ART during the chronic phase⁶⁴. Recent cohort studies^{65,66} have found no differences in clinical, immunological, or virological outcome in the short and medium term (3 years) among patients who initiated ART during acute infection and those who did so after acute infection (recent infection). Nevertheless, the immunological and virological outcome of both groups was better than that of patients with acute or recent infection who did not receive ART⁶⁵⁻⁶⁷.

RECOMMENDATIONS

- This committee considers that in clinical practice there is not sufficient scientific evidence to recommend ART to patients with acute HIV-1 infection. Therefore, ART is not recommended unless there are severe clinical manifestations or a prolonged duration of symptoms, once its advantages and disadvantages have been explained to the patient (level C). In the case of untreated patients, ART criteria should be re-assessed any time after

6 months, when infection is chronic. Furthermore, this committee recommends enrolling these patients in clinical trials to evaluate new therapeutic strategies. If a patient initiates ART, the same baseline ART regimens as for chronic infection must be followed (level C). In any case, a resistance test should be carried out previously because of the possibility of transmitting strains with resistance mutations (level B).

Chronic HIV-1 infection

ART-naïve patients

Treatment-naïve patients must be assessed on an individual basis as to when to initiate ART and which combination of drugs is to be used. The advantages and disadvantages of all the options must be carefully weighed up.

When to initiate ART

Triple ART, or HAART, has reduced the risk of progression and death of HIV-1-infected patients as the different combinations are sufficiently potent to reduce VL and lymphatic tissue to lasting undetectable limits and to enable the immune system to be restored, albeit partially^{10,13,18}. These spectacular results, which in patients at an early stage of chronic infection can return the immune system to "almost" normal levels, have been marred by the medium-to-long-term toxicity of antiretroviral drugs (ARD), adherence problems, resistance and the subsequent limitation of future therapeutic options, the possible transmission of resistant strains, drug-drug interactions, and the impact on quality of life^{15,44}.

The current debate centers on the criteria to be used to decide when is the best time to initiate ART. The most recent evidence seems to favor an early start, although it should be understood that the definition of early or late is totally arbitrary and has varied over time. At present, the limit between early and late has been set at 350 CD4+ lymphocytes/ μ L.

Data from observational studies⁶⁸⁻⁷⁹ suggest that:

1. The initiation of therapy should be based more on the CD4+ lymphocyte count than on VL. We must bear in mind that the depletion of CD4+ lymphocytes is faster when VL levels are higher; therefore, this should be monitored more closely in patients whose VL is higher. VL can help to take decisions in specific situations, particularly when the CD4+ lymphocyte figure is between 200 and 350 cells/ μ L.

2. In patients with a CD4+ lymphocyte figure below 200 cells/ μ L, the clinical benefit of receiving ART is clear. Waiting until CD4+ lymphocytes are below 200 cells/ μ L can expose the patient to the risk of opportunistic diseases.

3. No clear difference in immune and/or virological or clinical response has been observed between patients who initiate ART when their CD4+ lymphocytes are between 200 and 350 cells/ μ L and those who start therapy when the CD4+ lymphocyte figure is higher than 350 cells/ μ L, although more recent studies have shown a greater tendency (non-significant) towards progres-

sion to AIDS and death in patients who start ART when their CD4+ lymphocyte count is between 200 and 350 cells/ μ L (especially if the CD4 percentage is below 15%) than in those who start therapy with more than 350 cells/ μ L.

RECOMMENDATIONS

- The decision to start ART should be based on three elements: symptoms, CD4+ lymphocyte count, and VL.

- Patients with a symptomatic HIV-1 infection (events classed as B and C by the CDC)⁸⁰ should initiate ART in all cases (level A). If the patient has an acute opportunistic infection, ART can be delayed for a few weeks, clinical circumstances permitting.

- For patients with an asymptomatic infection, the time to start therapy will be based on the number of CD4+ lymphocytes/ μ L and on VL (table 2):

1. Patients with a CD4+ count of < 200 cells/ μ L should initiate ART (level A).

2. Patients with a CD4+ count of between 200 and 350 cells/ μ L should start ART in most cases (level B). Physicians should bear in mind that current evidence

TABLE 2. Indications for antiretroviral therapy in asymptomatic patients with chronic HIV infection

CD4 lymphocytes	Asymptomatic patients
< 200	Always recommend
200-350	Recommend on most occasions*
> 350	Defer

*In general, patients with a CD4+ lymphocyte count of between 200 and 350 cells/ μ L should initiate ART, especially if the proportion of CD4 is below 14%. However, in certain circumstances ART could be deferred: if the CD4+ lymphocyte remains stable at approximately 350 cells/ μ L and viral load is low (< 20,000 copies/ μ L).

tends to favor initiating ART closer to 350 cells/ μ L than to 200 cells/ μ L. Nevertheless, therapy could be delayed in those patients whose CD4+ lymphocytes remain stable at approximately 350 cells/ μ L and whose VL is low (more or less below 20,000 copies/mL).

3. Patients with a CD4+ of > 350 cells/ μ L can delay initiating therapy (level B).

TABLE 3. Combinations of antiretroviral therapy in treatment-naïve patients*

Possible combinations	Regimens		
Preferred regimens	One drug from column A + one from column B + one from column C		
	A ^a	B ^a	C ^b
	Tenofovir (TDF) Abacavir (ABC) Zidovudine (AZT)	Lamivudine (3TC) Emtricitabine (FTC)	Efavirenz Lopinavir/r Fosamprenavir/r
Alternative regimens	Didanosine (ddI) Stavudine (d4T)		Nevirapine Atazanavir/r** Saquinavir/r Atazanavir** Nelfinavir
	Regimen for when PI or NN cannot be used		
Contraindicated regimens	ABC + 3TC + AZT		
	Regimens with unboosted SQV Regimens with some combinations of NA (3) ABC + 3TC + TDF ddI + 3TC + TDF d4T + ddI + ABC		

*The table has been drawn up from the results of clinical trials and the majority consensus of the expert committee.

^aAvailable data suggest that 3TC and FTC can be used in the same way (level C). The NA combinations of choice as part of initial triple regimens are TDF + FTC (or 3TC), ABC + 3TC (or FTC) or AZT + 3TC (or FTC). The choice of each of these combinations will depend on the third drug chosen and the safety profile (level A). Of the 2-NA combinations of choice as part of initial triple regimens, TDF + FTC in combination with efavirenz has proven superior to AZT + 3TC. The latter combination is effective and with wide clinical experience. The order in which the drugs appear reflects the majority feeling of the experts. Depending on the third drug chosen, there are some NA combinations of choice with which there is no experience (ABC + 3TC with nevirapine, with lopinavir/r or with atazanavir/r). There is no experience with TDF + 3TC in combination with a PI as initial therapy, but there is with TDF + FTC (in combination with lopinavir/r). There is no experience with the combination TDF + 3TC plus nevirapine. The combination d4T + 3TC is efficacious, but alterations in lipid metabolism, lipodystrophy, and peripheral neuropathy mean that it is considered an alternative regimen. The combination d4T + ddI must be avoided due to toxicity, and it is not recommended during pregnancy (risk of severe lactic acidosis, with pancreatitis or hepatic steatosis). The combination TDF + ddI is not recommended due to its greater toxicity and lower efficacy.

^bIn one study, EFV was proven to have a lower risk of failure than LPV/r (level A). Fosamprenavir has proven to be non-inferior to LPV/r, but it has not been compared with EFV. This committee considers that the global risk/benefit balance favors EFV over NVP (level C). NVP shows greater toxicity and has not been tried with current NAs. **Atazanavir has not been approved (or evaluated) by the EMEA for treatment-naïve patients and its efficacy has been proven with AZT + 3TC. It can be administered comfortably (once daily) and seems to have a good lipid profile. It is preferable to use boosted PIs.

^cAZT + d4T, FTC + 3TC, TDF + ddI, ddI + d4T and any combination with ddC.

Consulting the text will make for a better interpretation of the table.

The time to initiate ART should always be decided on an individual basis taking previous considerations into account. Before the decision is made, at least two CD4+ and VL determinations should be performed to confirm the results. Furthermore, the patient should be prepared to initiate ART, by discussing the different options, trying to adapt the schedule of therapy to the patient's lifestyle, and evaluating the risk of poor adherence¹⁵.

Which combination of antiretroviral drugs should be used?

At present, the first-choice ART regimen is a combination of three drugs including two NAs and a boosted PI or an NN (table 3)¹⁻⁴. Most of these combinations allow a VL of < 50 copies/mL to be reached at 48 weeks in 60-70% of cases⁸¹.

These guidelines consider "preferential regimens" those that are backed by data from a larger number of long-term clinical trials, with optimal efficacy and durability, acceptable tolerability, and which are easy to use. "Alternative regimens" are considered to be those that have also proven their efficacy in clinical trials, but with a lower number of patients or for a shorter period of time, or which are less efficacious, more toxic, or more difficult to take. In any case, the choice of regimen must be made on an individual basis and must be based on the potential advantages and disadvantages. The following factors should be taken into account: degree of immunosuppression and baseline VL, adherence, regimen convenience, possible dietary restrictions, presence of comorbidity, type of secondary effects that may result in the short, medium and long terms, potential pharmacokinetic reactions and possible therapeutic options in the case of failure. At present, we have several regimens that are equally efficacious. In this context, this committee wishes to stress the growing importance of the cost of ART when setting up preferred treatment schedules.

With respect to the different combinations of ART, this committee wishes to make several points. First: most experience in patients with advanced immunosuppression (CD4+ lymphocyte count < 100 cells/ μ L) is with combinations of NAs with lopinavir/ritonavir (LPV/r) or efavirenz (EFV)⁸²⁻⁸⁶. Second: regimens composed of 3 NAs are less efficacious than regimens composed of 2 NAs + 1 NN⁸⁷ and there are data indicating that they are less efficacious than 2 NAs + 1 PI in patients with a very high VL²⁸⁸⁻⁸⁹. Third: there is little clinical experience with the combination of ART from the three families (NA, NN and PI); although this ART can be very potent, its complexity, toxicity and limited future therapeutic options in the case of failure mean that it cannot be recommended as initial therapy¹⁻⁴. The same is true for regimens including only two PIs¹⁻⁴. Fourth: the combination of an NN and a PI has proven to be as efficacious as triple therapy with PIs in a recent study⁸², although this was not the case in others⁹⁰, and it could even be more toxic in its impact on lipid metabolism^{91,92}. Fifth: fusion inhibitors (FI), such as enfuvirtide (T-20), are not used in initial therapy and should be kept for patients whose previous regimens have failed. Sixth: the evidence does not show that using more than three ARDs for initial therapy produces

better results than the traditional three-drug regimen⁹³⁻⁹⁵.

RECOMMENDATIONS

- For initial therapy, 2 NAs + EFV or 2 NA + 1 boosted PI can be used (the preferred NAs, boosted PIs and NNs are detailed in the following sections). The combination of 3 NAs (zidovudine + lamivudine + abacavir) is an alternative when the previous regimens cannot be used (level A) (table 3).

- For the naive patient beginning treatment, regimens based on one NN are generally better than regimens based on a boosted protease inhibitor (PI/r) with low-dose ritonavir (RTV): 1) High efficacy proven in numerous clinical trials, 2) Low pill burden (soon one pill) makes them easier to use, 3) Fewer serious pharmacokinetic interactions, 4) More favorable metabolic profile, 5) Lower cost. In addition to these advantages, it must be stressed that, thanks to their low genetic barrier, NNs are best indicated in treatment-naïve patients. The use of NNs in rescue regimens is compromised by a reduction in the activity of the other components of the regimen.

- The main advantage of PI/r is their high genetic barrier to the development of resistance. This high genetic barrier makes them more attractive than NNs in cases of primary resistance and in patients exposed to prolonged and repeated periods of non-adherence to ART⁹⁶.

Nucleoside analog reverse transcriptase inhibitors (NA) and nucleotide analogs (NtA)

In Spain, 7 NAs are commercialized: ZDV, didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), emtricitabine (FTC) and abacavir (ABC). One NtA, tenofovir DF (TDF), is also available. For practical purposes in these guidelines, the abbreviation NA includes TDF. ddC will shortly be taken off the market.

The combination of two NAs is included in most triple or quadruple therapies¹⁻⁴. The committee considers that the combinations of choice are TDF + FTC, ABC + 3TC and ZDV + 3TC, since their tolerance and efficacy have proven acceptable in several clinical trials. Furthermore, available data show that either FTC or 3TC can generally be administered. It must be stressed that these three combinations present very different toxicity profiles. ZDV has a greater risk of causing lipodystrophy than TDF⁹⁷⁻⁹⁸. Between 5% and 8% of patients treated with ABC develop a hypersensitivity reaction whose incidence will probably decrease with the genotyping of HLA-B*5701. Many reports of isolated cases and some cohort studies reveal deterioration in the renal function of patients exposed to TDF, which is generally associated with other nephrotoxic factors, although this has not been proven in clinical trials.

Combinations with ZDV + ddI and ddI + 3TC may be an alternative, although information is scarce. The only data on the combination ddI + FTC come from a clinical trial⁹⁹, therefore the safety profile of this combination has not been firmly established.

The combination d4T + 3TC has proven its efficacy in several clinical trials, but it is only considered as an alternative regimen today due to its greater toxicity. The combination d4T + ddI is not recommended due to its potential greater long-term toxicity and it is contraindicated (as

long as there are alternatives) in pregnant women due to the risk of severe, even fatal, lactic acidosis with pancreatitis or hepatic steatosis¹⁰⁰. The combination TDF + ddI must not be administered at all due to its greater toxicity and lower efficacy¹⁰¹⁻¹⁰⁵. The committee considers that ZCV + d4T should not be administered because of antagonism and that ddC should not be administered with any NA because of toxicity associated with ddC¹⁻⁴. Neither is it recommended to use FTC with 3TC, since they have a similar resistance profile and probably have few associated clinical benefits.

In any case, the final choice of combination of NA must be on an individual basis taking into account the characteristics of the drug, clinical situation, and patient preferences. Easy regimens can facilitate adherence. These include drugs that can be administered once daily (ABC, ddI, FTC, 3TC and TDF) or coformulated with fixed doses (e.g., TDF + FTC; ABC + 3TC; and ZDV + 3TC). Fixed dose combinations probably improve adherence, although it is arguable whether this advantage is clinically relevant¹⁰⁶.

The combination ZDV + 3TC is a simple, efficacious regimen with wide clinical experience. Its cost, in coformulated tablets, is lower than that of coformulations of TDF + FTC or ABC + 3TC. The combination ABC + 3TC is equivalent to ZDV + 3TC¹⁰⁷. There is no clinical trial experience with the combination ABC + 3TC with nevirapine (NVP) or with atazanavir (ATV). TDF + 3TC is efficacious in combination with EFV¹⁰⁸. No studies have been carried out on TDF and 3TC in combination with a PI as initial therapy, but there have been studies on TDF with FTC (in combination with lopinavir boosted with ritonavir [LPV/r])¹⁰⁹. The combination TDF + 3TC is more efficacious than AZT + 3TC when associated with EFV, although the difference seems to be due essentially to the lower toxicity of the former in the short term and medium term⁹⁸. There is no experience with the combination TDF + 3TC (or FTC) plus NVP. In general, it is reasonable to extrapolate the results obtained with 3TC to those obtained with FTC and vice versa (level C).

The combination ddI + FTC associated with EFV, is superior to ddI + d4T + EFV⁹⁹. There is no experience with the combinations ddI + FTC nor with NVP nor with PI. The combination d4T + 3TC has proven its efficacy in several studies, although it produces more alterations of lipid metabolism, lipodystrophy, and peripheral neuropathy than the combination TDF + 3TC¹⁰⁸. Therefore, the combination d4T + 3TC is considered an alternative regimen. In addition to TDF + 3TC or FTC, ABC + 3TC and ddI + FTC, other combinations of NA could be used in once-daily regimens, although their long-term virological efficacy has not yet been determined (ddI + 3TC)^{99,110}.

RECOMMENDATIONS

- The combinations of NAs and/or NtA of choice for initial triple regimens are TDF + FTC (or 3TC), ABC + 3TC (or FTC) or ZDV + 3TC (or FTC) (level A). The choice of one of each of these combinations will depend on the third drug chosen and on the safety profile (level A). Physicians must bear in mind that a clinical trial⁹⁸ has shown a greater risk of developing lipodystrophy in patients treated with ZDV than in patients treated with TDF (level A). Although there are no clinical trials that directly compare

the development of lipodystrophy in patients treated with ZDV or ABC, evidence from other trials^{111,112} suggests that ABC is similar to TDF with regard to the risk of developing lipodystrophy. Other alternatives are ddI + FTC or 3TC, d4T + 3TC and ZDV + ddI. Available data suggest that FTC and 3TC can be used indistinctly (level C). The combinations d4T + ddI and TDF + ddI must be avoided due to their toxicity and lower efficacy. The following combinations are not recommended: ZDV + d4T, 3TC + FTC and ddC + any other NA. Prudence is recommended with combinations of NAs and/or NtA that have not been studied in clinical trials.

ART combinations with three NA

Combinations of 3 NA have shown virological and immunological efficacy in several studies.

Although regimens with 3 NA are easier to take and have fewer drug-drug interactions than other combinations, several trials have shown that this regimen is less efficacious than regimens with NNs or PIs⁸⁸⁻⁸⁹. Therefore, the combination ZDV (or d4T) + 3TC + ABC should only be used in treatment-naïve patients as an alternative to a regimen with NN or with PI when these cannot be used due to problems of toxicity, interactions with other drugs, or complexity of the regimen. It is not recommended to use d4T + ddI + ABC as initial therapy¹¹³. Furthermore, combinations of 3 NAs that include ABC + 3TC + TDF or ddI + 3TC + TDF should not be used in any patient¹¹⁴⁻¹¹⁶.

The combination ZDV + 3TC + ABC is available in a commercial presentation that enables it to be administered in one tablet twice daily. This makes it an attractive regimen in terms of adherence.

RECOMMENDATIONS

- A regimen with ZDV + 3TC + ABC should only be used when it is not possible to use a regimen with NNs or PIs as initial therapy (level A). It is not recommended to use d4T + ddI + ABC as initial therapy (level A). The committee also recommends not using at any time 3-NA regimens containing ABC + 3TC + TDF or ddI + 3TC + TDF (level A). There is not enough experience to make recommendations with other combinations of 3 NAs and/or NtA.

Non-nucleoside reverse transcriptase inhibitors

Only two NNs are commercialized in Spain: NVP and EFV. Both drugs are cytochrome P450 inducers; therefore, they can cause pharmacokinetic interactions. EFV is administered once daily (one 600 mg capsule). This drug is contraindicated during pregnancy¹¹⁷. NVP should be administered as follows: one 200 mg tablet daily for 14 days and then one 200 mg tablet twice daily. In the 2NN study, NVP administered once daily seemed to be as efficacious as NVP twice daily, although the study was not powerful enough to evaluate the non-inferiority of NVP QD compared with EFV. Furthermore, greater liver toxicity was observed with this regimen¹¹⁸. These drugs must be used in potent combinations, since, if VL is not completely suppressed, there may appear mutations that induce cross-resistance to all the drugs in this family⁴⁴.

To date, it has been shown that regimens with EFV or NVP are more efficacious than those with 3 NAs^{87,88}. Fur-

thermore, several studies have shown that a regimen with EFV is more efficacious than a regimen with some PIs (indinavir [IDV]⁹⁰, nelfinavir [NFV]¹¹⁹, saquinavir boosted with ritonavir [SQV/r]¹²⁰, amprenavir boosted with ritonavir [APV/r]¹¹⁴, LPV/r⁸²). No studies have compared NVP or EFV with fosamprenavir (FPV/r). No clinical trials have shown that NVP is more efficacious than a PI. Finally, comparison of these two drugs has not enabled us to draw definite conclusions¹¹⁸.

In addition to these considerations, when choosing an NN the following should be taken into account: 1) EFV is contraindicated in pregnant women due to the risk of teratogenicity. It should also be avoided in women who do not use safe contraception or who wish to become pregnant. Similarly, it should be avoided in patients with a history of severe psychiatric conditions. EFV can produce dizziness, concentration disorders and/or somnolence. Patients should be informed that, if they present these symptoms, they should avoid potentially dangerous tasks such as driving or using machinery. 2) Severe, and even fatal liver events have been described with NVP; these occur during the first weeks of therapy. In addition to an increase in transaminases, approximately half the patients also develop cutaneous exanthema, with or without fever or flu-like symptoms. Therefore, NVP should be administered with extreme caution in patients with chronic liver disease and elevated transaminases, and it is contraindicated when transaminases are more than five times the upper limit of normal. The first 18 weeks of therapy with NVP are critical and require close monitoring of patients in order to spot the potential onset of severe cutaneous reactions (including the Stevens-Johnson syndrome and toxic epidermal necrolysis) that may be a risk to life or severe hepatitis/hepatic insufficiency. The greatest risk of these reactions appears during the first six weeks of therapy. However, the risk of hepatic problems remains after this period and monitoring should be continued at frequent intervals. Women and patients with a high CD4+ lymphocyte count have an increased risk of adverse liver reactions. A greater incidence of symptomatic liver problems has been observed in women with a CD4+ lymphocyte count of > 250 cells/ μ L compared with those who have a count of < 250 cells/ μ L (11% vs. 0.9%). Similarly, an increased risk has been reported in men with a CD4+ lymphocyte count > 400 cells/ μ L compared with those who have lower counts (6.3% vs. 1.2%). In some cases, liver damage has progressed despite discontinuation of therapy. Patients who develop signs or symptoms of hepatitis, severe cutaneous reaction, or hypersensitivity reaction must interrupt therapy with NVP. Therapy with NVP should not be re-initiated after severe hypersensitivity, cutaneous, or liver reactions. Liver tests should be monitored every two weeks for the first two months of therapy, at the third month, and regularly thereafter. This monitoring of liver tests should be closer if patients present signs or symptoms suggestive of hepatitis and/or hypersensitivity or if GOT or GPT values are \geq 2.5 times the upper limit of normal before or during therapy. NVP should not be administered to patients with GOT or GPT values > 5 times the upper limit of normal before therapy until baseline GOT/GPT values stabilize (Viramune, SPC). Special care must be taken with EFV and NVP in

patients on methadone, since their dose of methadone usually has to be increased.

RECOMMENDATIONS

- This committee considers that the global risk/benefit balance prefers EFV to NVP (level C). The choice of a drug should take into account the risks associated with specific toxicity. NVP is not recommended in women with a CD4+ lymphocyte count of > 250 cells/ μ L or in men with a count of > 400 cells/ μ L. NVP should be used with extreme caution in patients affected by hepatotropic viruses.

Protease inhibitors

In Spain, 8 PI are commercialized: saquinavir (SQV), indinavir (IDV), ritonavir (RTV), nelfinavir (NFV), fosamprenavir (FPV), lopinavir (LPV), atazanavir (ATV) and tipranavir (TPV). ATV boosted with ritonavir and TPV boosted with ritonavir are only approved by the EMEA for treatment-experienced patients. PIs are cytochrome P450 inhibitors, and can therefore cause pharmacokinetic interactions. They are included in triple regimens with two NAs, these triple combinations being the ones with which there is more experience^{6,8}. The final choice of PI is based on efficacy, tolerance, interactions, posology and pharmacokinetics.

Full-dose IDV, NFV and RTV should only be used in treatment-naïve patients in exceptional cases owing to their lower efficacy and/or greater toxicity and/or greater complexity of use. This committee recommends habitual use of RTV-boosted PIs for treatment-naïve patients.

FPV is a prodrug of amprenavir, which makes it possible to reduce the number of daily capsules both when used as the only PI (two 700 mg capsules BID) and when boosted with RTV (one 700 mg capsule + 1 ritonavir capsule BID, or two 700 mg capsules + 2 ritonavir capsules QD, although the latter dosage may be less efficacious, especially in rescue regimens). The dose of FPV recommended by the EMEA is 700 mg BID with 100 mg of RTV BID.

ATV is an azapeptide PI that is administered once daily. The recommended dose of ATV is 300 mg (it is presented in 100 mg, 150 mg and 200 mg hard-gel capsules—300 mg capsules will soon be available) administered with 100 mg of RTV once daily with meals. It has fewer adverse metabolic effects than other PI, particularly when taken unboosted with RTV. Blood levels of ATV are reduced when administered with EFV or TDF. The doses of ATV/r are 400/100 mg when taken with EFV and 300/100 when combined with TDF.

ART combinations that include boosted PI

The use of small doses of RTV (the PI with the strongest cytochrome P450 inhibitory effect) inhibits the metabolism of the second PI and improves its pharmacokinetic profile. The combination of a PI boosted with RTV makes it possible to reduce the pill burden and use once-daily or twice-daily dosing with meals, which favors adherence to ART. Furthermore, it improves the C_{min}/C_{I50} ratio of the second PI. Thus, resistance could be avoided. These combinations of PI have the disadvantage that they can boost toxicity.

LPV/r was the first fixed-dose coformulation of 2 PIs, and its virological and immunological efficacy has been

maintained in a seven-year study^{35,121}. Once-daily LPV/r (6 capsules) has proven to be as efficacious as administration every 12 hours, although with a greater frequency of diarrhea¹⁰⁹. To date, it has been administered in three capsules (400 mg/100 mg) every 12 hours. The EMEA has approved a new pharmaceutical formulation of LPV/r in coformulated tablets containing 200 mg of LPV and 50 of RTV. The recommended dose is two tablets every 12 hours. Pharmacokinetic data support a lower interindividual variability in the plasma concentrations of lopinavir and a lesser effect of food intake¹²². Furthermore, with this new presentation, it is not necessary to refrigerate the tablets, even if they are to be stored for more than one month (RTV must be kept in the refrigerator if it is to be stored for more than 30 days or if the room temperature is higher than 25 °C). No data are available yet on the tolerance/toxicity of the new tablets compared with the capsules.

In treatment-naïve patients, studies¹²³⁻¹³⁰ show that a PI (LPV, SQV, FPV, ATV) boosted with RTV has efficacy and barrier advantages against the development of resistance compared with unboosted PI. The main disadvantage of boosting with RTV is the increased risk of adverse effects, but this is compensated by a marked increase in its antiviral potency and in the genetic barrier against resistance.

RECOMMENDATIONS

- The committee recommends LPV/r and FPV/r as first-choice PIs (level A). Both have a similar antiviral activity and metabolic and tolerance profile. ATV/r and SQV/r are alternatives, and, although they can be as efficacious as LPV/r (level C), this committee considers them as alternatives until comparative data from clinical trials with LPV/r become available. TPV/r should not be used in treatment-naïve patients (level A).

Treatment-experienced patients

The usual reasons for changing ART are therapeutic failure, toxicity or intolerance, lack of adherence, or simplification of a complex regimen. In this section, we shall discuss the scientific evidence supporting the current recommendations on the modification of ART in a patient whose therapy is failing. The remaining reasons for modifying ART are discussed in other sections of these Guidelines and in the extended document available on the web pages of GESIDA and the PNS.

Failure of ART

The failure of ART can be defined from a clinical, immunological, and virological standpoint. The criteria for each of these types of failure have been described in section 2. Unless stated otherwise, when we speak of therapeutic failure, we are referring to virological failure.

The incidence of therapeutic failure, its causes, and the profile of selected resistance mutations have changed over the 10-year history of ART. The early ART period (1996-1999) was characterized by a generalized use of complex and toxic combinations of NAs and unboosted PIs in patients who had often received suboptimal therapy with NAs. Observational studies that analyzed the appearance of virological failure during the early years of

ART reported 20% to 60% incidence in patients taking their first ART^{27,131,132}. Some patients who currently suffer from multi-resistant HIV-1 infection are from this period. Since 1999 (recent ART) and coinciding with the introduction of NNs and PIs boosted with low doses of RTV (PI/r), the incidence and characteristics of the failure of early ART have changed substantially. Several studies show a lower incidence of therapeutic failures after the introduction of NNs as a component of ART¹³³⁻¹³⁴. The modern ART era shows a generalized preference for very simple regimens combining non-thymidine NAs and NNs or PI/r, all of which will lead to a change in the profile of the selected resistance mutations during the first virological failure, i.e., it will reduce the incidence of thymidine analog mutations (TAMs) and mutations of the protease gene, by increasing resistance mutations against NNs, i.e., K65R selected by TDF and ABC, L74V selected by ABC and, especially, M184V¹³⁵.

Factors affecting therapeutic failure

The factors affecting failure of ART are very diverse although they can be classified in 3 broad groups depending on the patient, drugs, or the virus. In the first group, adherence to treatment is the most important and has been identified as an excellent predictor of therapeutic response, both in the context of clinical trials and in cohort studies¹³⁶⁻¹³⁸.

The most important drug-dependent factor is the potency of the regimen. Other factors are defective absorption of the drug and pharmacological interactions.

The most important virus-dependent factor is resistance to antiretroviral drugs as a result the enormous replication capacity of HIV-1, its wide diversity, and pharmacological pressure. Resistance to antiretroviral drugs can be transmitted to other people and can be detected in up to 12% of recent HIV-1 infections^{138,140}.

Two cohort studies published a few years ago agree that if a VL of < 50 copies/mL is reached after the first ART, a rebound in VL is usually associated with poor adherence or with adverse reactions, and very rarely with a genuine failure of therapy, i.e., due to a lack of potency, drug-drug interactions, or problems of absorption^{40,141}.

Criteria for changing ART due to therapeutic failure

Decisions on whether to change therapy because of failure are usually based on virological criteria (Section 2), except in the particular situation of a patient with multi-resistant HIV-1 infection (see below). As a general principle, in the case of a virological failure, therapy should be changed as soon as possible to avoid an accumulation of mutations and an increase in VL, thus facilitating the response to new treatment.

In some patients with ART and suppressed VL, rebounds or transitory elevations of VL (blips) can be observed just above the threshold for detection. In most studies, these rebounds are not associated with a greater risk of failure^{39,41,42,142}, and can appear in combined therapy with NNs or PIs¹⁴³. Nevertheless, the study with the greatest number of patients, carried out in the Frankfurt and Swiss cohorts, found that 704 of 2055 patients with efficacious ART developed blips (490 with one episode and

155 with two episodes). In patients who suffered a rebound, the risk of virological failure was two times greater than in those patients who maintained a suppressed VL, whereas in those who had two consecutive determinations of VL of between 50 and 500 copies of RNA/mL, the risk of failure increased more than five-fold³⁸. The discrepant results of these studies may be due to the number of patients included, length of follow-up, the periodicity of the VL determinations, or to differences in the study populations. These same reasons could explain why, in some studies, there is a genetic evolution of HIV-1 and selection of resistance to antiretroviral drugs during blips^{41,142}.

Immunological failure (see Section 2) is usually preceded by virological failure. Occasionally, some patients with undetectable VL maintain a decreased CD4+ lymphocyte count. In these cases ART should not be changed, except for combinations leading to a decrease in the number of CD4+ lymphocytes, e.g., TDF + ddI. Treatment with IL-2 should be considered^{144,145}.

Clinical failure in a patient taking ART, i.e., the appearance of clinical B or C events associated with progression of HIV-1 infection, is not always associated with virological failure. These events sometimes appear after the first months of ART in very immunodepressed patients, or are associated with immune restoration. Tuberculosis or the malignant lymphoproliferative processes¹⁴⁶ that are often diagnosed in HIV-1-infected patients can oblige efficacious ART to be modified in order to avoid the pharmacological reactions and toxicity that are common to the different drugs the patient has to take.

TABLE 4. Possible therapeutic regimens in patients who experience virological failure after their first ART regimen

Previous regimen	New regimen
3 NAs	2 NAs ^a + NN or PI/r ^{b, c} 1 or 2 NAs ^a + NN + PI/r ^{b, c}
2 NAs + 1 NN	2 NAs ^a + PI/r ^{b, c}
2 NAs + PI or PI/r ^b	2 NAs ^a + 1 NN ^d 2 NAs ^a + PI/r ^{b, c, e} 1 or 2 NAs ^a + 1 NN ^d + PI/r ^{b, c, e}

^aThe choice of new NA must be based on a resistance test.

^bAdministration of a PI/r improves the pharmacokinetics of the PI, reduces the incidence of mutations of resistance to PI, and facilitates adherence.

^cThe choice of PI must be based on a resistance test.

^dIn a previous failure with NA in patients naive for NN, inclusion of an NN (efavirenz) in the new therapy improves the virological response.

^eWhen a PI/r is used in the initial regimen and the diagnosis of virological failure is early, mutations may not be detected in the protease gene. In this case, the 2 NAs must be changed. The PI/r can be maintained unless there is intolerance, toxicity or poor adherence.

NA: nucleoside/nucleotide analog reverse transcriptase inhibitor;

NN: non-nucleoside reverse transcriptase inhibitor;

PI/r: protease inhibitor boosted with ritonavir.

General recommendations on changing ART due to virological failure

- A change in ART due to failure must be made early in order to avoid the accumulation of mutations and an increase in VL, thus facilitating the response to new therapy (level C). The only exception to this recommendation is multi-resistant HIV-1 infection.

- In the case of virological failure, a resistance test should be carried out to design the best therapeutic regimen (level B). The resistance test should be carried out while the patient is receiving the failed therapy or during the 4 weeks after its discontinuation.

- The choice of new ART after therapeutic failure makes it necessary to analyze the causes, especially when the failure is due to adherence to ART or drug-drug interactions. The results of previous resistance tests (if any) should be taken into account, the complete pharmacological history should be known, and any possible toxicity to specific antiretroviral drugs should be noted (level C).

- Transitory elevations in VL of between 50 and 500 copies of viral RNA (blips) do not make it necessary for ART to be changed (level B).

Change of ART after the first failure (second-line therapy)

Few randomized clinical trials have evaluated the efficacy of the different combinations of antiretroviral drugs in second-line therapy.

The objective of therapy in this situation is to achieve a resuppression of VL. Therefore, the change in ART should not be delayed, resistance testing should be performed¹⁴⁷, and three active drugs should be introduced depending on the results.

The following situations can occur depending on initial ART: failure with 3 NA, with 2 NAs and 1 NN or with 2 NAs and one PI (table 4).

Change to ART after the first failure of a regimen containing 3 NAs

No randomized trials have tackled this problem. In patients who fail after initial therapy with ZDV, 3TC and ABC, the most common mutation is M184V⁸⁷. Patients who have initiated ART with 3 non-thymidine NAs often develop mutation M184V and can select K65R^{135,148,149}. In these cases, two thymidine analogs (ZDV and d4T), NNs and PIs remain active. Furthermore, it is well known that patients with previous failures to NAs are hypersusceptible to EFV, which favors the virological response if we add this drug to the new treatment¹⁵⁰. An ART regimen with 2 active NAs in the resistance test with an NN and a boosted PI can be efficacious in this situation of failure. Therapy with four drugs (2NAs, 1NN and 1PI), while possibly more efficacious, runs the risk of having greater toxicity, worse adherence, and fewer future possibilities of rescue.

RECOMMENDATIONS

Second-line therapy in this situation of virological failure would be:

- Two new NAs (chosen depending the result of the resistance tests) with 1 NN (level C) or a PI boosted with RTV (level C), or with an NN and a PI, preferably boosted with RTV (level C). If the latter option is chosen, we must bear in mind that adherence can be more difficult.

Change of ART after the first failure of a regimen containing 2 NAs and 1 NN

NNs, especially EFV, are the most widely used drugs in initial ART. A single mutation (e.g., 103N) is capable of generating high-level resistance to one or all NNs, which usually occurs when there is incomplete suppression of HIV-1 replication¹⁵¹. This is often accompanied by other mutations conferring resistance to NA (basically M184V, and, less commonly, TAMs, L74V or K65R).

RECOMMENDATIONS

- The most reasonable therapy is a regimen with 2 new NAs (depending on the resistance test) and a PI boosted with RTV (level C). This option has proven to have antiviral efficacy in patients who have already been treated with 2 NAs, and therefore these drugs are expected to have a similar effect in patients treated with 2 NAs and 1 NN.

Change in ART after the first failure with a PI-containing regimen

During the early ART era, failure with 2 NAs and 1 PI occurred frequently, either due to toxicity or poor adherence¹⁵². Fortunately, the currently generalized use of PI/r has reduced the incidence of virological failure when an initial PI is used.

PIs are slightly different with respect to the other antiretrovirals and this has important implications for the development of therapeutic failure. First, the efficacy of PIs may depend on pharmacokinetic factors^{153,154}. Second, the development of resistance to PIs is a gradual process that normally requires the accumulation of several mutations in the protease gene¹⁵⁵, which may confer class resistance to PIs. The appearance of resistance is an ongoing phenomenon that leads to progressive reduced susceptibility of viral strains to PIs. There are also mutations selected by some PIs that do not present cross-resistance with others: 30N (NFV)¹⁵⁶, and 50L (ATV)¹⁵⁷.

The combination of a PIs (LPV, SQV, IDV, APV, FPV, ATV and TPV) with low doses of RTV can increase the plasma concentration of the PI, improve dosing and adherence, and reduce the incidence of mutations of resistance to PIs¹⁵⁸. The introduction of a fixed-dose combination of LPV/r in the year 2000 proved very efficacious in patients with a history of therapeutic failures with NNs or PIs. Undetectable and durable VL was achieved in a significant number of patients^{159,160}. Furthermore, when virological failure is detected in a patient receiving a regimen containing boosted PIs, mutations may not be detected in the protease gene, although they may be detected in the reverse transcriptase gene^{35,161}.

The use of a second boosted PI may be a valid alternative as second-line therapy, especially if the change is made quickly and the accumulation of numerous mutations in the protease gene is not permitted^{1,162}.

Another simple and efficacious regimen consists of a combination of 2 new NAs and 1 NNs. The lack of cross-resistance between PIs and NNs, as well as hypersusceptibility to NNs in patients with a certain degree of resistance to NAs¹⁵⁰ speak in favor of this combination as second-line therapy after a first failure with a PI. Several studies have shown that, in patients exposed to PIs and NAs and not exposed to NNs, the inclusion of an NN in the new therapy improves the virological response¹⁶³. If this option is chosen, the 2 NAs must be totally active and with a high genetic barrier, since an incomplete suppression of VL would lead to a rapid selection of mutations conferring resistance to NNs.

RECOMMENDATIONS

Second-line therapy in this situation of failure would involve the following:

- Two new NAs (chosen depending on the results of the resistance test) and 1 NN. This option may be attractive for patients with serious adherence problems (level C).
- Two new NAs (chosen depending on the results of the resistance test) and a PI/r. This option would be limited to situations that do not involve mutations of resistance to the new therapy (level C).
- One or two new NAs (chosen depending on the results of the resistance test) with a second PI/r and an NN. This alternative is indicated for patients who have not had adherence problems and in whom failure has been caused mainly by problems of antiviral potency, pharmacokinetics, or resistance (level C). NAs and PIs should be chosen according to the results of the resistance test.

Change of ART after more than one therapeutic failure (rescue therapy)

Definition

Treatment after failure of at least two lines of ART is known as rescue therapy. In this situation, and with the exception of those patients who started therapy with 3 NAs, most patients have experienced failure with the three most common families of antiretroviral drugs: NAs, NNs and PIs.

Objective of therapy

The objective of therapy in this population is to achieve once again maximum viral suppression (< 50-400 copies/mL). Therefore, there must be at least two active drugs in the new regimen, which must also contain other previously used drugs that conserve some activity in the resistance test and are well tolerated by the patient. This objective is currently possible with the new drugs available, although the percentage of successes falls as the number of accumulated failures increases.

In this situation, it is important not to delay the change in therapy, since continued use of the failed regimen only helps to increase VL and accumulate a greater number of mutations in the protease and reverse transcriptase genes. Several strategies help achieve resuppression of VL:

- *Make adherence easy.* New ART must be comfortable and well tolerated. In patients with multiple failures of therapy due to difficulties of adherence, the administration of simple regimens, such as ZDV/3TC/ABC + TDF, can achieve unexpected results¹⁶⁴. Furthermore, directly observed treatment strategies, which are currently available thanks to the large number of QD regimens, may prove useful in specific populations^{165,166}.

- *Resistance testing.* A genotypic or phenotypic resistance test with each virological failure can optimize the new treatment, increase its efficacy, and improve prognosis¹⁶⁷.

- *Genotypic inhibitory quotient.* The development of resistance to PI is progressive and related to the successive accumulation of mutations in the protease gene. The increase in mutations requires an increase in the concentration of the drug necessary to suppress viral replication. The genotypic inhibitory quotient (GIQ) is the ratio of the plasma concentration of the drug to the number of relevant mutations in the protease gene, and is currently considered a predictive marker of response to therapy with PIs. In general, having > 5 mutations in the protease gene significantly reduces the efficacy of PI/r¹⁶⁸.

- *Monitoring of drugs in plasma.* The interindividual variability of the plasma concentrations reached with PI and the interactions between antiretroviral drugs and other active ingredients mean that, occasionally, the expected plasma levels are not reached. This is especially important in rescue therapies, which use several antiretroviral drugs with unknown pharmacokinetic interactions that can lead to an insufficient plasma concentration. Therefore, monitoring of drugs in plasma can improve the efficacy of treatment¹⁶⁹, e.g., with 2 boosted PIs, and may require dose adjustment⁶². It may also be useful if the objective is to increase the PI dose in order to increase its inhibitory quotient¹⁷⁰.

None of these strategies has been evaluated in prospective and randomized studies with sufficient statistical power to enable them to be recommended in daily clinical practice.

ALTERNATIVES IN RESCUE THERAPY

In recent years, several clinical trials have compared different rescue therapies. These studies cannot be easily compared due to the heterogeneous nature of the study populations, the diversity of previously used drugs, the efficacy criteria used and follow-up time. Most experience has been with the new boosted PI and with T-20. Furthermore, there is interesting experience with 2 PIs boosted with RTV. With very few exceptions, NNs have not proven useful in this situation.

Boosted protease inhibitors specifically indicated for rescue therapy: *Tipranavir.* This is a non-peptide PI with potent in vitro activity against HIV-1 strains that are resistant to currently approved PIs¹⁷¹. This drug has recently been approved in Spain and is indicated for HIV-1-infected patients who have received several antiretroviral drugs and who are carriers of viral populations that are resistant to various PIs. The approved dose is 500 mg BID in combination with RTV 200 mg BID.

The antiviral efficacy of TPV has been proven in two phase III studies with an identical design: RESIST-1 with 630 patients in North and South America, and RESIST-2 with 876 patients in Europe and Australia¹⁷².

TPV boosted with low doses of RTV is efficacious for reaching the therapeutic objective marked in this situation, especially if it is associated with T-20. Its main disadvantage is its greater liver and metabolic toxicity than other available PI/r¹⁷².

Darunavir (TMC114). This PI, which has not yet been approved by the European Agency for the Evaluation of Medicinal Products, but which is available in many Spanish centers through expanded access programs, has been specially designed to be active against HIV-1 strains with mutations in the protease gene¹⁷³. Two clinical trials (POWER 1 and 2) in phase IIb have evaluated the efficacy and tolerance of different doses of TMC114 boosted with RTV against a comparator boosted PI (CPIr), both combined with other antiretroviral drugs according to a resistance test. The patients included should have been treated previously with NAs, NNs and PIs, and they should have presented at least one primary mutation in the protease gene and a VL of > 1000 copies/mL. We now have the results of 110 patients followed up until week 48; they reveal a greater efficacy of TMC114 against the comparator PI. A VL of < 50 copies/mL was observed in 46% of those who received darunavir compared with 10% of those who received the comparator PI. When T-20 was added, 58% of patients in the TMC114 arm had an undetectable VL compared with 11% in the other arm. The increase in CD4 was 102 compared with 19 cells/ μ L¹⁷⁴. The proposed dose of TMC114 is 600mg boosted with 100 mg of de RTV every 12h. To date, the efficacy of darunavir as a rescue therapy has not been compared with that of TPV.

Another clinical trial, POWER 3 (with inclusion criteria and baseline characteristics similar to those of POWER 1 and 2) included 327 patients and was designed to extend the safety and tolerability database, although the efficacy of the drug was also measured. The data of this study corroborate the results of POWER 1 and 2 at 48 weeks. All three studies showed that darunavir seems to be well tolerated, the most common adverse effects being nausea and headache. It also seems to show a better hepatic profile than CPIr and a lipid profile similar to that of CPIr¹⁷⁵.

Recently, 11 genotypic mutations have been identified (V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V, L89V), and they have been associated with reduced sensitivity to TMC114 in more than 9,600 samples from different clinical trials with multitreated patients. The presence of 3 or more of these mutations at baseline was associated with a lower percentage of patients with an undetectable VL at week 24, although the percentage of patients with an undetectable VL was greater than in the control arm. With only one or two of these baseline mutations, the percentage of patients with a VL < 50 copies/mL was 57% and 46%, respectively, in the TMC114/r arm. The presence of 3 of these mutations was associated with a high number of mutations (greater than or equal to 9) in other positions of the protease gene¹⁷⁶.

Enfuvirtide (T-20). T-20 acts by inhibiting the fusion of HIV-1 with human cells and preventing the virus from entering them and starting its replication process. It is administered subcutaneously and its main adverse effect is a local reaction at the point of injection. Two phase III studies (TORO I and TORO II) compared the antiviral activity of T-20 as part of an optimized ART regimen with an optimized ART regimen not containing T-20. The studies included almost 1000 multi-treated patients (75% with previous AIDS) between them, with a median baseline VL > 100,000 copies/mL and a median CD4+ < 100 cells/ μ L. At 24 weeks, the fall in VL was significantly greater in the patients treated with T-20 than in the patients treated with the optimized ART regimen only. T-20 produced an additional fall in VL of $-0.93 \log_{10}$ in the TORO I study and of $-0.78 \log_{10}$ in TORO II ($p < 0.0001$)^{177,178}. In the combined analysis of both studies, the fall in VL at week 48 compared with baseline was $-1.48 \log_{10}$ copies/mL for the group that received T-20 compared with $-0.63 \log_{10}$ copies/mL for those who received the optimized therapy only ($p < 0.0001$)¹⁷⁹. The probability of reaching a virological response, regardless of the definition used, was more than double in patients treated from the start of the study with T-20 compared with the control group: the fall in VL > 1 \log_{10} was 37% compared with 17%; VL < 400 copies/mL was 30% compared with 12%; and VL < 50 copies/mL was 18% compared with 8% ($p < 0.0001$). Time to failure was almost triple in the T-20 group compared with the control group, 32 and 11 weeks, respectively ($p < 0.0001$)¹⁸⁰. That is, not only the primary efficacy analysis, but also all the secondary efficacy analyses predefined in the study design showed that rescue therapy in multitreated patients was more efficacious with regimens based on the combination of T-20 and drugs selected according to resistance testing.

In addition to the factors for virological efficacy defined elsewhere¹⁸¹, the response at week 12 helps to predict the response to therapy¹⁸². In a modified on-treatment analysis (all those patients who continue on treatment at weeks 24, 48 and 96 are evaluated), all those patients who achieved a fall $\geq 1 \log_{10}$ at week 12, 59.5% (95%CI: 53.8%-65.1%) maintained a VL < 400 copies at weeks 96, and 39.2% (95%CI: 33.6%-44.8%) maintained a VL < 50 copies, compared with 2.6% (95%CI: 0%-6.1%) and 1.3% (95%CI: 0-3.8%), respectively, in patients with no virological response at week 12.

Mutations that reduce sensitivity to T-20 have been identified in gp41 of the virus, therefore, we can expect future studies to report a correlation between specific mutations and virological response to T-20^{177,178}.

In summary, T-20 is the drug of choice in patients with several accumulated resistance mutations. A recent Spanish consensus on the use of T-20, whose conclusions are pending publication, recommends using it in those patients for whom an optimal 3-drug regimen cannot be designed.

Two boosted protease inhibitors. These regimens essentially consist of the combination of LPV/r with another PI, thus taking advantage of the small dose of RTV contained in the commercial combination of LPV/r which also boosts the second PI. Although attractive in theory, few studies support these combinations as rescue therapy.

Lopinavir and saquinavir. This combination is attractive because of the intrinsic potency of both drugs and thanks to the low pill burden of the new pharmaceutical presentation of SQV in 500 mg hard-gel capsules. Several studies show that there are no significant changes in the plasma concentrations of LPV and SQV when they are administered together with RTV^{183,184}.

Lopinavir and fosamprenavir. There is a significant interaction between LPV/r and FPV that leads to a fall in the concentrations of both drugs^{185,186}. The clinical importance of these findings is not known with any accuracy; therefore, these drugs should not be used in combination.

Lopinavir and atazanavir. One study analyzed the pharmacokinetic and efficacy profile of the combination of LPV/r (400/100mg BID) plus ATV (300 mg QD) in 16 patients with few therapeutic options¹⁸⁷. This combination achieved high plasma concentrations of both PIs, with a low toxicity potential (no patient had to suspend therapy) and high virological efficacy. At 24 weeks, 13/16 patients presented a VL of < 50 copies. If these results are confirmed, this combination could prove attractive.

Recommendations on rescue therapy

- With currently available drugs, it is possible to achieve an undetectable VL in a high number of patients (level A). The objective of rescue therapy is to achieve once again an undetectable VL (level C).

- It is recommended to use at least two new antiretrovirals that are totally active according to the resistance test and from different pharmacological classes. These two drugs will be administered with others that the patient may have already received, but that maintain a certain degree of antiviral activity (level A).

- In patients who accumulate several resistance mutations in the protease and reverse transcriptase gene, it is advisable to carry out a genotyping study, consult updated databases on internet, or ask an expert in treating patients experiencing virological failure. In this situation, TPV/r or TMC114/r plus T-20 plus recycled antiretroviral drugs are the regimens that achieve the best results (level A).

- The new ART regimen should be comfortable, well tolerated, and as minimally toxic as possible. Adherence to therapy should be guaranteed before starting rescue therapy (level C).

Treatment of HIV-1 infection in the patient with no therapeutic options

We define HIV-1 infection as multiresistant or with no therapeutic options when it is impossible to design an ART regimen that is potentially efficacious with currently available drugs or with those that will become available in the near future.

In this population, where achieving suppression of VL is very difficult or impossible, the objective of therapy will be to preserve the immune function and avoid clinical progression of the infection. Obtaining CD4+ lymphocyte counts of > 200/ μ L or a fall of at least 0.5 \log_{10} in VL is considered successful, since it is usually accompanied by a slowing-down of clinical progression.

In general, virological failure in the multi-treated patient rarely leads quickly to clinical and immunological failure^{132,188,189}. In fact, many patients experiencing viro-

logical failure maintain stable or even greater CD4+ counts, and approximately only one third experience a fall to counts below baseline values¹⁹⁰.

In cases where it is impossible to design a regimen with at least two potentially efficacious drugs, it is reasonable to aspire to a limited fall in VL which allows maintenance or immunological improvement and, therefore, avoidance of clinical failure while waiting for new therapeutic options^{191,192}. The possibility must be considered of referring these patients to a center with experimental drugs in clinical trials.

Therapy with ≥ 5 antiretroviral drugs ("mega-HAART")

One option for rescue therapy that aims for complete suppression of viral replication is combination therapy with five or more drugs, which has become known as "mega-HAART" (e.g. 2 boosted PIs + 2-3 NAs \pm NNs). Except for anecdotal studies, "mega-HAART" regimens have not shown any clinical benefit, are difficult to fulfill, have high toxicity and are expensive.

Suspension of ART in patients with multiple therapeutic failures

Several studies have analyzed the usefulness of temporary interruptions of ART based on the hypothesis that the reappearance of the wild-type sensitive to the drugs will facilitate a better response after reintroducing therapy. Clinical trials performed to evaluate this strategy show a marked fall in the CD4+ lymphocyte count during the interruption compared with those of patients who continue with ART and have a greater risk of clinical progression.

Therapy with non-suppressive ART

Several studies have shown the beneficial effects of maintaining an ART regimen that does not suppress VL (when compared with total suspension of therapy) in patients with multi-resistant HIV-1 infection, especially if they have advanced HIV-1 infection.

In patients with no options for therapy, non-suppressive treatment that does not compromise the efficacy of future drugs can be chosen. Treatments that are comfortable, minimally toxic, and that somehow reduce viral capacity to replicate must be sought.

In these patients it is tempting to use ART with 3TC or FTC in order to select mutation M184V in the majority viral strain, either alone or in combination with 1 or 2 NAs that the patient can tolerate without difficulty, thus enabling viral replicatory capacity to be reduced¹⁹³.

Introduction of new antiretroviral drugs in advanced clinical trials

The best therapeutic option in multi-resistant HIV-1 infection would involve the availability of new drugs aimed at new therapeutic targets and, thus, active against HIV-1. Very often, the patient's immunological status and the appearance of new antiretroviral drugs do not allow us to wait until two active drugs are available and oblige us to introduce a new drug to a new antiretroviral regimen in which the other drugs are recovered, i.e. monotherapy. Nevertheless, for a patient with severe immunodepression (CD4+ < 100/ μ L) and the risk of clinical progression and death, the new drug should be introduced, since this in-

volves a transitory improvement in the patient's immunological status.

Recommendations in multi-resistant HIV-1 infection

- It is not recommended to interrupt therapy, especially if the CD4+ lymphocyte count is ≤ 200 -250/ μ L (level A).

- When there is a risk of clinical progression or death and it is not possible to design therapy with two active drugs over a short period of time, ART should be administered, even if it only includes one active drug (level C). These therapies can lead to a transitory improvement in immunodeficiency and improve prognosis. The possibility of referring the patient to a center with experimental drugs should be considered.

- All treatment options for multi-resistant HIV-1 infection should contain 3TC or FTC in order to select and maintain mutation M184V, and thus reduce the capacity for viral replication (level C). If optimal therapy is not possible, it is advisable to maintain a suboptimal treatment. In this case, it is also indicated to maintain 3TC or FTC.

Simplification of efficacious ART

Simplification of ART is understood as changing a regimen with which absolute virological suppression has been achieved for another that maintains this suppression and that allows the regimen's complexity to be reduced. Thus, both the patient's quality of life and adherence can be improved. The objectives of simplification are to maintain virological and immunological control, improve adherence and quality of life, and to prevent, improve, or resolve some of the secondary effects of ART.

The reasons for modifying and simplifying ART are as follows: to reduce the pill burden and frequency of administration (combinations are now available that can be administered once daily), eliminate dietary restrictions, improve current or potential toxicity, reduce the risk of interactions and take advantage of new formulations, new indications, or new drugs.

Given its advantages, simplification of ART has frequently been requested by patients who have achieved virological suppression with a complex regimen, and it has been the object of a recent review by GESIDA¹⁹⁴. This strategy began to be used with the appearance of the NNs, simpler drugs, with fewer secondary effects and an efficacy similar to that of the PIs available at the time. Most simplification studies have been carried out starting with regimens containing unboosted PIs. The use of low-dose RTV as a booster of other PIs, the new formulations of older PIs such as SQV and the new generations of PI such as LPV, ATV and FPV, have enabled us to design PI-containing regimens that do not present the problems of complexity and tolerance observed with first-generation PIs. Therefore, simplification starting with these regimens may not be as necessary as before.

ART can be simplified by reducing the number of drugs, pills, or doses, all of which has been shown to improve adherence⁸¹.

Reducing the number of drugs

The first ART simplification studies aimed to reduce the number of drugs in what came to be known as the induction-maintenance strategy. This strategy involved a first

induction phase with three or four antiretrovirals followed by a maintenance phase with fewer than three drugs.

These first studies did not manage to maintain virological control by using fewer than three drugs.¹⁹⁵⁻¹⁹⁷ Some of the possible reasons for the failure of the maintenance regimens used could be an excessively short induction time (3 to 6 months), a VL limit that was too high to start a maintenance regimen (200 or 500 copies/mL), the inclusion of patients with possible resistance to one of the drugs, or the lower potency of the combination of only two drugs¹⁹⁸. Therefore, the failure of these studies is probably due more to their design than to the fact that the strategy itself was erroneous.

Recently, the strategy of simplifying to monotherapy with LPV/r has begun to be studied, after having achieved virological suppression during an induction period with triple therapy including this drug¹⁹⁹. This approach is justified by the potency of the drug and by the apparent absence of resistance to it when the regimens containing it fail. Therefore, eventual rescue of a failure would not be compromised. The results of a randomized clinical trial including 198 patients followed up for 48 weeks shows the viability of this strategy, although more follow-up and experience is necessary before it can be recommended in clinical practice²⁰⁰.

This same strategy is being explored with ATV/r, although the only study available at the moment is a pilot study with a limited number of patients and no control arm²⁰¹.

Reduction of pill burden and/or number of doses.

Pill burden and/or number of doses can usually be reduced when a drug from another group substitutes the PI from the previous regimen. In this strategy, which has been widely studied, three drugs have been evaluated for substituting the PI: EFV, NVP and ABC.

There is evidence that the stable virological suppression and immunological improvement achieved with a regimen including one or several PI are adequately maintained or even improve when the PI is switched to EFV, NVP or ABC.

The advantages of this strategy include an improvement in quality of life and adherence, and in some cases, a reduction in secondary effects, especially those related to the lipid profile. The improvement in lipid profile has been observed more intensely in the different studies in which simplification has been to NVP or with abacavi²⁰².

In patients with no previous failure of NA, there are no notable differences in efficacy between the three drugs used when substituting the PI. In patients with a previous failure on NAs or previous suboptimal therapy, a greater number of virological failures has been observed due to accumulation of mutations of resistance to NAs, a fact that is most observed in the group of patients who simplify to abacavi.

In those cases where the wish is to maintain the PI, it is possible to simplify to unboosted ATV (or boosted ATV if it is combined with TDF)²⁰³.

RECOMMENDATIONS

- In patients with no previous failure with NAs or previous therapy with NAs in monotherapy or bitherapy, treatment can be simplified indiscriminately to EFV, NVP, ABC or ATV (level A).

- It is not recommended to simplify to ABC when there are previous suboptimal treatments with NAs (level A). Simplification to ABC combined with TDF and 3TC or to TDF and dDI is contraindicated (level B).

- In patients with an undetectable VL in their first regimen, it is possible to simplify to a QD regimen consisting of dDI + F'CTC + EFV, TDF + 3TC + EFV and, probably, to dDI + 3TC + EFV (level A).

- Other possible combinations should be made in the framework of clinical trials and not, for the moment, in habitual clinical practice (level C).

Conclusion

This document has updated the latest data from publications or communications at scientific meetings on antiretroviral therapy. Given the characteristics of the document, the content has been reduced substantially. Previous recommendations examined integral antiretroviral therapy in the seropositive patient (with or without other concomitant conditions, pregnancy, etc.), in addition to drug adverse effects, pharmacokinetic interactions, and post-exposure prophylaxis. This information can be found in a more extensive document on the web pages of GESIDA and PNS.

Recommendations of GESIDA/Spanish AIDS Plan on antiretroviral

Coordinators: José López Aldeguer, Federico Pulido, Rosa Polo.

Members (in alphabetical order): Antonio Antela, Jose R. Arribas, Julio Arrizabalaga, Juan Berenguer, Bonaventura Clotet, M.^a José Galindo, José M.^a Gatell, Juan González García, José Antonio Iribarren, José María Kindelán, Pablo Labarga, Fernando Lozano, Esteban Martínez, Celia Miralles, José M.^a Miró Meda, Santiago Moreno, Daniel Podzamczar, Joaquín Portilla, Esteban Ribera, Melcior Riera, Antonio Rivero, Rafael Rubio, Jesús Santos, Juan Miguel Santamaría, Jesús Sanz, Ferran Segura, Vicente Soriano, Montserrat Tuset, Pompeyo Viciano.

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