

FRENCH EXPERTS GROUP'S  
RECOMMENDATIONS FOR MEDICAL  
MANAGEMENT OF HIV INFECTION

HIGHLIGHTS AND  
RECOMMENDATIONS

2006

## FRENCH GUIDELINES

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## INTRODUCTION

Since 2004, the year of the last report, clinical care of HIV infection has evolved; the 2006 report underlines this evolution.

From epidemiological data, the estimated number of individuals living with HIV infection is around 130,000 to 150,000. Approximately 7,000 new contaminations are reported annually. The frequency of contamination is increasing among men who have sex with men, in part due to a relaxation of sexual practices. People originating from sub-Saharan African countries account for half of newly reported cases, underlying the need to ensure access to care in this frequently underprivileged population. Contrary to current recommendations, 50 % of HIV-infected patients start antiretroviral therapy at an already severe immune deficiency stage or during AIDS, often because they were not aware of their HIV status at the time of AIDS diagnosis. Late referrals are associated with a poorer outcome, this difference remaining significant several years after initiation of therapy. These data have not improved since 2004. They underline the necessity of prevention and testing campaigns targeting the most exposed populations.

Despite these worrying observations, the constant improvement of HIV therapy has to be emphasized. Without loss of efficacy (65 % of treated patients are in virological success), it has improved in terms of simplicity (number of pills) and tolerance. This has allowed a shift in the recommendation of when to start antiretroviral therapy towards an earlier stage of HIV infection (CD4 cell count of  $350/\text{mm}^3$ ). In addition, new drugs are more active than previously available ones on multiresistant viruses. Given ongoing efforts, there is a reasonable hope of further improvements in the medium term. The objectives of antiretroviral therapy have been recently refined. In addition to an undetectable plasma viral load, reaching and maintaining a CD4 cell count higher than  $500/\text{mm}^3$  is an important objective, because this level is associated with a life expectancy similar to that observed in the general population.

However, treatment of HIV infection remains complex, because of risks of drug side effects and virus resistance limiting antiviral activity. Genotypic resistance tests constantly improve and now include data pertaining to drugs made recently available. Their indications have become wider, but interpretation of the tests results is often complex. Indications and technical conditions of drug

concentration monitoring in the plasma are better defined, and the results of these tests contribute to an optimisation of the efficacy/safety ratio of therapy by the clinician. Despite numerous improvements, antiretroviral drugs remain toxic: lipodystrophy and metabolic complications (mostly lipid abnormalities with the associated cardio-vascular risks), are major and frequent issues, difficult to treat and justifying constant prevention efforts to avoid an increase in mortality/morbidity due to therapy, in sharp contrast with a decrease in virus-related mortality/morbidity.

Causes of death, in HIV infected patients, are more diverse in 2005 than previously reported: AIDS is directly involved in approximately one third of cases.; Most frequently reported other causes are cancers, cardio-vascular diseases, suicide or viral hepatitis. More attention should be given to HCV co-infections, because they accounted for 11 % of deaths in HIV-infected patients in 2005. HCV infection is present in more than 25 % of HIV-infected patients, but only slightly more than half of them had a correct HCV work-out in 2004. It is, therefore, urgent to reinforce recommendations for HCV testing, and for organizing complex anti-hepatitis therapy in co-operation with hepatologists. The validation, in co-infected patients, of non-invasive tests for staging of liver disease, will probably improve clinical care by making the practice of liver biopsy less frequent.

In the field of infections and cancers, associated directly or indirectly with AIDS and responsible for morbidity and mortality in HIV-infected patients, the emphasis is now on prevention. It is still the case that one third of patients with a CD4 cell count less than  $200/\text{mm}^3$  do not receive pneumocystis prophylaxis. Detection of complications (such as HIV related cognitive impairment, cervical dysplasia in women, and anal lesions), and specialist-oriented clinical care for lymphoma or cancer, remain fundamental, given their higher incidence than in the general population, without any recent improvement.

The rate of viral transmission from mother to child remains very low, and both pregnant women and children benefit from recently available drugs. Unfortunately, drug presentations are often not adapted young children. Medically assisted conception remains a cumbersome path for couples with HIV infection in man or woman, but conditions of access and procedures are better defined ; 200 children were born since the first studies were started and 11 centres for medically assisted conception are open to such couples.

The estimated number of HIV-infected children in France is 1500 in 2005 ; 10 to 20 new cases are reported annually. Given the improved efficacy of

antiretroviral therapy, almost no death has been reported in children during the past two to three years. However, when getting older, these children become aware of their social stigmatisation which exacerbates teenage problems. They may require specific support with the aim of, for example, improving compliance to therapy and discussing issues of sexuality and prevention.

Infections with M group HIV-1 from non B subtype (the most prevalent subtype in the West) now account for 40 % of reported new cases in France, and are particularly observed in patients originating from sub-Saharan African countries. Infections with HIV-2 and HIV-1 from non-M groups are rare in France. Data are still lacking on the natural history of such infections, on the activity of antiretroviral drugs and on changes under therapy.

For many reasons, some of them being discussed above, the clinical care of HIV infected persons is evolving, becoming global with the combination of therapeutic, psychological, preventive and social approaches. This is why a number of professional groups are involved, together with the HIV specialist, to contribute to the patient's care. In addition to clinicians from various medical specialities, psychologists, social workers and HIV activists play an important role. Improving adherence to therapy, a necessary condition for treatment success difficult to maintain by the patient due to drugs constraints and sometimes psychological and social context, is a good example of how important multidisciplinary care is. To incorporate the increased complexity of patient care, the idea of an annual multidisciplinary work-out has been put forward, performed at best in a day-care hospital ; but ways of financing this activity remain to be decided.

A chapter on organization of care concludes this report. The 2002 report contributed to initiate a discussion that has just been concluded with the constitution of COREVIH (a regional coordination of actors fighting HIV infection). This structure replaces the previous one (CISIH), non longer adapted to the evolution of the disease characteristics. COREVIH are aimed at improving the link between prevention, testing and care, between hospital and non-hospital care, and will facilitate the global, multidisciplinary and interprofessional approaches which have been so often emphasised in this report. Activists will contribute to this coordination. Whether the amount of COREVIH financing will allow them to fulfil their missions remains to be seen.

This chapter addresses HIV prevention, testing, medical care , and the socio-legal issues pertinent to health cover and access for recent migrants and

prisoners in French jails.

Changes in clinical care of HIV infection have been characterised by treatment improvements and a global approach to care, and should continue in the same direction. Clinical research, although not addressed in this report, cannot be separated from medical care and will contribute dynamically to clinical evolution, as has always been the case in France. Within hospitals, funding for research deserves to be ensured.

The initial recommendations for the medical care of HIV-infected patients were drawn-up in 1990, at the request of the French Ministry of Health. Successive updates, achieved by experts firstly under the leadership of Jean Dormont then Jean-François Delfraissy, have been instrumental in helping health professionals to incorporate changes in treatment strategies and patient care into daily practice. Once again, many experts have contributed to this report. Their enthusiasm in achieving this activity, in addition to their numerous responsibilities, is acknowledged.

Patrick Yeni

## STRENGTH OF RECOMMENDATIONS

A	Strong evidence to support the recommendation
B	Moderate evidence to support the recommendation
C	<u>Insufficient evidence to support the recommendation</u>

## QUALITY OF EVIDENCE RATING SCALE

Ia,b*	At least 1 randomized clinical trials; meta analysis of randomized clinical trials
IIa,b	non randomized clinical trials; cohorts or case-control studies; meta-analysis of cohorts or case-control studies
III	Expert opinion

Roman numeral reflects the nature of the evidence supporting the recommendations

\*a= published in the peer-reviewed literature; b= presented in abstract form at peer-reviewed scientific meetings



## EPIDEMIOLOGY

### Highlights

France has conducted a national survey regarding not only the incidence and prevalence of HIV infection but also the characteristics of the disease in HIV patients included in the French data base (FHDH) whether they are on treatment or not.

At the end of 2003, prevalence of HIV infection was estimated by back calculation as 106 000 with a plausible interval of 88 000 to 185 000. It is increasing by about 3500 cases per year.

In 2004, the number of new diagnosis of HIV infections was estimated as 7000. Exhaustivity is nearly 63 per cent. Heterosexual intercourse represents the predominant route of transmission among patients discovering their HIV positive status in 2004. Fifty per cent originated from sub-Saharan Africa. Epidemic continues in men infected through homosexual contacts. HIV transmission in intravenous drug users remained low.

Half of the patients who are eligible to start antiretroviral therapy according to the 2004 French guidelines are seen at an advanced stage of the disease (AIDS or lymphocyte CD4 count below 200/ml)

Nearly 65 % of patients monitored in the FHDH achieved viral goal (viral load below 500 copies/ml). Severe treatment failure ( $CD4 < 200/mm^3$  and viral load  $> 30\,000$  copies/ml) was seen in 4%.

Morbidity and mortality are variable because of patients ageing, high frequency of cardio vascular and cancer risk factors, HIV infection itself or treatment-related side effects.

In patients with viral success and CD4 lymphocytes count over  $500/mm^3$ , survival is similar to the unaffected population

The proportion of patients seen at later stage of the disease has not changed much is similar between 1997 and 2004 (34%). The relative risk mortality remained higher for 4 years.

**The expert group's recommendations are :**

To report all new diagnosis of HIV infection

To develop new statistical models to improve assessment of HIV incidence.

To use these recommendations as standard of care guidelines in order to evaluate their impact on the quality of management of HIV infection and on patients survival in France.

To maintain measures to improve treatment access and management of patients living in the French West Indies.

To develop strategies:

- To improve serological diagnosis testing at an early stage of the disease in men who have sex with men, African immigrants and patients over 50 years old.
- To decrease the proportion of patients seen at a later phase and the rate of lost to follow up.

To closely monitor patients seen at a later stage taking into account to the current high death rate and to develop new therapeutic approaches for these patients.

To initiate prophylaxis against pneumocystosis and toxoplasmosis in patients with CD4 lymphocytes count below  $200/\text{mm}^3$ .

To improve multidisciplinary management of patients because of the observed diverse morbidity and mortality using the newly formed Regional Committee for HIV (COREVIH). Smoking, cardiovascular, neoplasia risk factors and psychiatric diseases should be taken in consideration in HIV-infected patients.

To achieve a lymphocyte CD4 count  $> 500/\text{mm}^3$  in all patients to decrease the over mortality rate.

## ANTI RETROVIRAL THERAPY

### Highlights

Initiation of antiretroviral therapy should be worked on by a multidisciplinary team approach to improve treatment adherence (AIII).

The goals of antiretroviral therapy are to achieve and maintain plasma viral load below 50 copies /ml and lymphocyte CD4 count over 200/mm<sup>3</sup> (A).

There is no benefit in stopping antiretroviral treatment. In patients who have a good treatment response, viral replication rebound occurs rapidly after interruption. The decrease in lymphocyte CD4 count is higher in patients who had a lower CD4 count prior to therapy (AIIa).

Persistence of viral replication (> 500 copies/ml) during treatment exposes patients to viral accumulation of resistant mutations which compromise future therapeutic options (AIIb) and is deleterious on CD4 lymphocytes count (AIIa).

Therapeutic viral failures should be discussed during multidisciplinary team meetings (AIII). Expert advice is required in cases of limited therapeutic options (AIII).

### The expert group's recommendations are:

#### **Regarding the first line antiretroviral regimen**

In symptomatic patients\* start antiretroviral therapy as soon as possible, taking into account opportunistic infection therapy and potential drugs-drugs interactions (AIa).

*\*major opportunistic infections, group C complications or recurrent group B manifestations, 1993 CDC classification.*

In asymptomatic patients with a CD4 lymphocyte count below 200/mm<sup>3</sup>, start therapy immediately (AIa).

In asymptomatic patients with CD4 lymphocyte count over 200/mm<sup>3</sup>:

Consider starting antiretroviral therapy when the CD4 lymphocytes count

is approaching 350/mm<sup>3</sup> (AIIa).

Do not start therapy in patients with CD4 lymphocytes count over 350/mm<sup>3</sup> except for those with a plasma viral load > 100 000 copies/ml (AIIa).

Include in the therapeutic regimen 2 NRTIs + 1 PI/r or 2 NRTIs + 1 NNRTI (AIa).

- For a PI/r-based regimen: (abacavir or tenofovir or zidovudin) + (emtricitabin or lamivudin) + (fosamprenavir or lopinavir or saquinavir) (AIa).
- For an NNRTI-based regimen: (abacavir or didanosin or tenofovir or zidovudin) + (emtricitabin or lamivudin) + efavirenz (AIa)

### **In patients successfully treated with a first line regimen**

Consider changing therapy only if the viral load is less than 50 copies/ml for at least 6 months (AIII) and do not introduce a drug which has previously generated side effects or where there is evidence of previously identified resistance mutations (AIa).

### **If simplification of first line PI-based regimen is required for tolerance and/or adherence issues**

Consider active combination of 2 NRTIs and 1 NNRTI capable of improving the lipid profile (AIa).

Do not use a 3 NRTIs-regimen in patients who have experienced treatment failures to prior therapy including NRTIs (AIa). This strategy may only be envisaged, after careful case by case consideration, in patients who have never experienced treatment failure, when the expected benefit is evaluated as greater than the risk of viral failure (BIa).

Do not use 1 NNRTI + 1 PI in patients who have no side effects (AIa).

Never use intermittent interruption strategies except in clinical trials (AIa).

### **In patients who do not achieve viral load suppression**

Whatever the stage of therapeutic failure, aim for a viral load below 50 copies/ml even after multiple drug failure (AIII).

Analyze the conditions of viral failure, taking into account clinical status, CD4

lymphocyte count and plasma viral load, adherence, tolerance and potential drugs-drugs interactions (AIII).

The optimal treatment regimen should be based on a complete clinical history and genotypic resistance testing while on therapy (AIIa). Results of prior genotypic resistance testing (AIII) and therapeutic drug monitoring are also important (BIII).

When genotypic resistance testing evidences no mutation, adherence should be a priority using TDM as a guide (BIII).

Associate at least two untried efficient drugs, ideally including one of a newer class (AIIa).

In patients presenting multiple drug failure or resistance to the three main classes (NNRTIs, NRTIs, PIs), the addition of enfuvirtide to active PI/r could be helpful in achieving an undetectable viral load (AIa).

When only one drug is active and the lymphocytes CD4 count is below  $200/\text{mm}^3$ , try to optimize therapy by adjusting drug dose (increased PI dosing for example ) using TDM (AIII).

Do not interrupt treatment strategy for any period of time (AIa).

## MANAGEMENT OF PATIENTS LIVING WITH HIV

### Highlights

Patient care from the start must not be limited to viral suppression but must integrate social, psychological and preventive aspects. Before initiating antiretroviral therapy, clinical, immune, viral, metabolic and other cardiovascular risk factors should be carefully evaluated.

Follow up of treated patients is complex and must be monitored by a specialised hospital team and a trained primary health care physician.

Adherence is an essential element in therapeutic success. Declared side effects and depression are among the major factors which negatively influence adherence. Structured interventions to improve adherence to ARV therapy have been shown to be efficient.

Recent epidemiological and behavioral data have shown that 1) understanding the quality of emotional and sexual life is important and 2) that the need to reduce HIV transmission through sexual contact is still a major issue.

Besides booster vaccinations, travelers' vaccinations and more specific vaccination (pneumococcus, flu) should be considered in patients with a CD4 lymphocyte count over  $200/\text{mm}^3$ ,

**The expert group's recommendations are (A):**

During the initial consultations a patient's general health and background should be evaluated.

Inform patients about therapeutic goals and the frequency and nature of potential side effects when ARV therapy is proposed.

Perform an annual work up, most probably in an hospital day care center, followed by a consultation with a specialist.

Promote the training of healthcare teams in adherence support and care.

Promote educational support consultations in health care establishments and health care networks.

Promote medical education programs with general practitioners with a view to optimizing long term management.

Perform gynecological and proctologic examinations during follow up.

Promote open discussion about sexual habits and the desire for parenthood.

Weigh up the benefits against the risks of vaccinations in severely immuno-compromised patients. It is often preferable to wait for an improvement in immune status before vaccination.

## PROCREATION AND HIV INFECTION

### HIV TESTING

#### Highlights

HIV screening during pregnancy

HIV testing should be systematically offered to informed and consenting pregnant women according to French health policy rules.

#### The expert group's recommendations are:

To perform a second test during the second trimester in women exposed to high risk of infection particularly if the partner is HIV-positive or of unknown status.

To offer a HIV testing to the future father

### PARENTHOOD

#### Highlights

HIV infected people should feel free to discuss their desire to become parents. They should receive information and counseling about their legitimate desire to have a child. Both partners must be clearly informed.

A hepatologist should be included in the medical team for patients presenting a co-infection with hepatitis B or C.

#### The expert group's recommendations are:

Discourage HIV patients who wish to have child from having unprotected sex To promote auto insemination methods in HIV-infected women to prevent viral transmission to her HIV negative partner.

To select antiretrovirals which are not contra-indicated during pregnancy

### PREGNANCY

## **Highlights**

Pregnancy in HIV infected women should be managed by a multidisciplinary team.

Prevention of mother-to-child transmission of HIV (MTCTV) has two objectives: 1) achieving a complete viral suppression i.e. an undetectable viral load 2) limiting drug-related side effects while preserving future therapeutic options in mothers.

The risk of HIV-1 mother to child transmission is 0.3 per cent when the viral load is below 50 copies/ml.

In HIV-treated women, failures of prevention are observed notably when the plasma viral load is high during labor and/or when the period of treatment has been short.

Antiretroviral related-drug toxicity in pregnant women remains an important concern and particular attention is required for the newest compounds.

### **The expert group's recommendations are:**

To provide information and counseling to women and their partners weighing up the risk /benefit of materno-foetal prophylaxis (AIII).

In women treated prior to pregnancy, continue their active antiretroviral regimen if successful and well tolerated (AIII).

To start therapy for the prevention of HIV materno-foetal transmission at the end of the second trimester (28 weeks), or even earlier if the viral load is high or if there is a higher risk of prematurity (BIIa).

To initiate a PI-based regimen including two NRTIs (AIIa) preferably with well tried drugs, in particular NRTIs (zidovudin+ lamivudin) (AIIa) and numerous PIs.

Do not use either a a) stavudin+didanosin combination (lactic acidosis risk in mother) or b) efavirenz (malformation) or c) nevirapin at the beginning of gestation (immuno-allergy) (AI).

Promote therapeutic adhesion with a closely monitored follow up where needed by providing nursing and psychological support, if necessary by at-home midwife care or hospitalization (AIII).



Declare all perinatal expositions to more recently available drugs to the authorities (AIII).

Do not systematically perform caesarean section in women receiving HAART with a viral load below 50 copies/ml at the end of gestation.(BIIa); caesarean section may be considered if the viral load is over 400 copies/ml.

To include a hepatologist in the health care team when women are co infected with hepatitis C or B (AII).

Ensure that women will be referred to a gynecologist for specific management and contraception (AIII) after delivery and in the longer term.

### **CHILDREN BORN FROM HIV INFECTED MOTHERS**

#### **The expert group's recommendations are:**

In the absence of high risk transmission, initiate a post natal prophylaxis as a standard of care with a zidovudin monotherapy regimen.

Consider an intensified regimen as soon as possible for:

Mothers who have not received PMTCT as recommended (AIa).

When the period of ARV therapy is less than 8 weeks (BIIa).

Mothers with a viral load (BIIa) of over 1000 copies/ml at spontaneous delivery or 10 000 copies/ml at cesarean section.

Prematurity (less than 35 weeks of gestation)

In all cases, expert advice is required

In full term infants, use a nelfinavir-based regimen in combination with zidovudin + lamivudin for 6 weeks as intensified therapy (AIIa).

Consider newborn hospitalization if treated with HAART (AIII).

Take into account potential maternal resistance virus mutations when treating infants (AIII).

Initiate a national prospective study regarding intensified therapy in newborns (AIII).

Explain that maternal breast feeding is not feasible (AII).

Perform vaccinations as recommended for the general population excepting the BCG. BCG could be performed when the HIV status of the child is definite. Do not initiate prophylaxis against opportunistic infections with TMP-SMX (BIII)

Use PCR ADN or ARN methods for diagnosis in children child under 18 months old.

Genotypic resistance testing should be performed in all infected infants.

## **MEDICALLY ASSISTED PROCREATION**

### **Highlights**

The two goals of the AMP are to:

Procreate without risk of HIV transmission in couples  
Treat infertility in either partner, male or female, or both, if HIV-infected

When the man is HIV-infected, there have been no reports of transmission during AMP treatment, in either his partner or child.

Waiting lists or constraints for attending AMP are similar to the general infertile population

When AMP is feasible, 50% of couples can hope to have a child, but the success rate decreases with the woman's age

Antiretroviral therapy is not necessary before AMP.

Changes in the rules regarding AMP are being reviewed by the French Biomedecine Agency.

### **The expert group's recommendations are(A III):**

Specialist centers should provide easy access to all available AMP methods for couples whether one or both partners are HIV-infected.

Always include a hepatologist within the multidisciplinary health care team in patients co-infected with hepatitis B or C.

## HIV INFECTION IN CHILDREN AND ADOLESCENTS

### Highlights

In 2005, the number of HIV-infected children was estimated as around 1500.

Ten to 20 new-born HIV-infections are diagnosed per year in France.

About one hundred adolescents are newly HIV-infected each year in France.

Knowledge about therapy in HIV-infected children is extrapolated from adult treatment experience.

Social stigmatization of HIV infected children still constitutes psychological handicap.

Telling children that they are HIV infected is a progressive process which depends on the age and other more individual characteristics of the child.

### The experts group's recommendations are :

To initiate therapy when CD4/CD8 ratio approaches 15% in all HIV-infected children (symptomatic or not ) (AIIa). For some members of the expert panel, the ratio limit could reach 20 per cent for children under 3 years old (BIII).

To offer, as first line therapy, a PI/r -based regimen including two NRTIs (abacavir+lamivudin or zidovudin+abacavir or zidovudin+lamivudin) (AIIa).

To perform TDM for some antiretrovirals, particularly for nelfinavir and other drugs not approved by the French agency for drug products, (BIIa) and in patients presenting with resistant viral mutations (Ia).

Not to interrupt therapy except for intolerance, poor adherence, patient's wishes, or for clinical trial purposes (Ia).

To refer HIV-infected children to specialist care centers (AIII). Accredited centers of excellence do not exist in France, as in other European countries. This option should be the subject of serious consideration.

Encourage the pharmaceutical industry to promote research for new pediatric ARV formulations appropriate for children. (AIII).

To discuss sexuality early in HIV-infected adolescents (AIII).

To reinforce prevention intervention programs regarding HIV disease in young people, particularly at school and to promote the use of anonymous and free HIV screening centers(AIII).

## ACUTE HIV INFECTION

### Highlights

In 2004 in France, 23 per cent of newly HIV infected individuals were in acute infection phase and half of them were infected through homosexual contacts.

The risk of disease progression in naive patients is significant when the CD4 lymphocytes count is less than  $500/\text{mm}^3$  during acute HIV infection phase. Close follow up is needed without delay.

### The experts group's recommendations are:

To systematically perform HIV serologic testing when sexually transmitted disease (STD) occurs and behavioral risk factors have been observed and to encourage HIV serologic testing in partners (CII).

To perform genotypic resistance testing in any HIV acute infection (BII).

To rapidly start a PI/r-based regimen in patients presenting with marked and persistent symptoms and/or with severe immune deficiency (CD4 lymphocytes count less than  $350/\text{mm}^3$ ) (AII). Treatment of 18 to 24 months duration can be proposed until immune goal is achieved (CD4 lymphocytes count over  $500/\text{mm}^3$ ) (BII). Re-starting therapy will depend on the CD4 lymphocyte count according to the chronic phase infection therapeutic guidelines (AI).

To emphasize the higher rate of HIV transmission during the acute infection phase and the importance of behavior modification (AIII).

To encourage inclusion of patients in acute infection phase in clinical trials and cohorts to improve therapeutic and epidemiological data analysis (AIII).

## ANTI RETROVIRAL RESISTANCE

### Highlights

Mechanisms and kinetics of resistant mutation acquisition differ in each of the antiretroviral classes (AIIa).

The selection of resistant mutations may be avoided by keeping viral load below detection level (AIIa).

Genotypic resistance testing is the key to assess treatment strategies. Multidisciplinary team (clinicians, virologists, and pharmacologists) discussion is needed for choosing an efficient regimen after prior treatment failure.

The resistance algorithm for genotypic resistance testing analysis is periodically updated. The following site should be consulted for the latest recommendations: <http://www.hivfrenchresistance.org>

Virologists play a major role in analysis of algorithm results mainly when resistance is considered as "possible" or when data regarding newest compounds are not yet validated.

### The expert group's recommendations are:

To perform genotypic resistance testing in newly diagnosed patients or, if not available, on the oldest blood sample prior to initiation of therapy (AIIa).

To perform genotypic resistance testing in patients presenting acute HIV Infection (AIIa).

To perform genotypic resistance testing in treated-patients who have not achieved full viral suppression (AIIa).

To identify the VIH-1 subtype using phylogenetic analysis of the reverse transcriptase sequence (AIIa).

## ANTI RETROVIRAL PHARMACOLOGY

### Highlights

PIs are boosted with low-dose ritonavir (PI/r) which improve their pharmacokinetic properties and their residual concentrations well above the IC<sub>90</sub> of wild-type sensitive viruses.

Combination of PIs with CYP3A metabolized drugs with a narrow therapeutic margin should be limited.

Simvastatin and atorvastatin (lipid-lowering agents) are contra indicated.

Methadone blood levels are decreased by PI/r induction.

### The expert group's recommendations are:

To perform therapeutic drug monitoring (TDM)(PI/r and/or NNRTIs) (B) in the following situations: therapeutic failure (AIII), drug interactions (AII), liver failure or co-infections with hepatitis C or B (AII), children (AII), pregnancy (BIII). TDM results should be discussed by a multidisciplinary team (physicians, pharmacologists, virologists...).

To quickly control the eventual consequences of the adjusted drug dosing on viral load.

To encourage relationship assessment between pharmacokinetic parameters, efficacy and tolerance for the newly available antiretrovirals.



## HEPATITIS VIRUS COINFECTIONS

### Highlights

#### *Hepatitis C Virus (HCV)*

Only 58% of hepatitis B virus (HBV) or hepatitis C virus (HCV) co infected patients have been assessed for liver fibrosis and nearly half of them have been treated.

Evaluation of liver damage by non invasive testing might be helpful in patient management in reducing the number of liver biopsies.

Educational support for the patient and his family, social and professional assessment, anticipation and treatment of drugs-related side effects enhance adherence

#### *Hepatitis B Virus (HBV)*

Prevalence of chronic hepatitis B in HIV-infected patients was estimated as 7%

HIV infection negatively influences the course and prognosis of chronic hepatitis B

Virus B eradication is not achievable with currently available treatment. Long term duration of therapy is the rule.

Treatment strategies for chronic hepatitis B in HIV-infected patients are based on antiretroviral indications.

### The expert group's recommendations are:

#### **In all patients**

To develop prevention programs in order to reduce continued HCV transmission in drug users and men who have sex with men (AIIa).

To routinely perform serologic testing for HCV and HBV in new diagnosed HIV patients and to repeat it periodically (at least annually) in uninfected subjects with ongoing high risk behavior (AIIa)

To vaccinate against HBV in non immunized patients (AIIa) and against hepatitis A virus (HAV) in chronically infected patients with HBV or HCV (AIIa).

To initiate therapy through a multidisciplinary team (AIII).

To assess liver damage and fibrosis with one or more non invasive testing tools and, if available, with the elastometry method. When concordant, liver biopsy is not helpful but when evidence is contradictory, liver biopsy should be considered (BIIa).

To refer severe cirrhotic patients to an hepatologist and to a liver transplantation center before the first decompensation (AIIb).

### **In patients with HCV**

To offer wide access to treatment in all HIV-infected patients (AIII).

To treat acute hepatitis C with pegylated interferon (PEG-IFN) plus ribavirin for 24 or 48 weeks if HCV RNA do not spontaneously disappear within 3 months following infection (AIIa).

To treat chronic hepatitis C with PEG-IFN plus ribavirin for 48 weeks if indicated (AIIa).

To avoid didanosin and to use zidovudin and stavudin cautiously in patients currently treated with antiretroviral therapy (AIa).

To use leukocytes growth factors (neutrophil count  $< 600/\text{mm}^3$ ) and erythropoietin (Hb  $< 10.5\text{g/dl}$ ) if necessary to optimize dosing and duration of antiviral C therapy.

To determine the HCV viral load at weeks 4 and 12 and stop treatment when the HCV-RNA has not significantly decreased ( $> 2$  log) in patients with moderate liver disease (AIIa). Antifibrotic therapy with PEG-IFN should be offer in nonresponders patients with severe liver damage but in clinical trials only (AIII).

To consider re-treatment with PEG-IFN +/- ribavirin in patients experienced a first antiviral C treatment failure.

### **In patients with HBV**

To determine anti-delta antibody in all HbS-antigen-positive patients (AIII).

No to use drugs with dual activity against HIV and HBV (lamivudin, emtricitabin, tenofovir) for treating HBV if an antiretroviral treatment against HIV is not indicated (AIII).

To use drugs which have dual activity against HBV and HIV when treating HIV/HBV coinfection. (AIII). Lamivudin or emtricitabin monotherapy regimen is not recommended to treat HBV-infection (AIIa).

To never stop HAART containing a drug active against HBV without ensuring treatment by another drug active against HBV (AIIa).

To assess periodically HBV viral load in treated patients. An increase of viral load more than one log cp/ml should lead to evidence a resistance mutation and change therapy against HBV (AIIa).

## COMPLICATIONS OF ANTIRETROVIRAL THERAPY

### Highlights

Metabolic disturbances are identified as consequences of antiretroviral therapy and take part in the lipodystrophy syndrome and cardiovascular disease risk factors

Prevalence of lipodystrophy remains high

Lipoatrophy is due to some thymidinic NRTIs (stavudin and in lesser extent, zidovudin). Exclusion of these drugs from therapeutic regimen leads to decrease the risk of occurrence of lipoatrophy.

Lipoatrophy is an important psychological concern for patients. Corrective interventions especially for facial lipoatrophy should be offered.

Statins are standard treatment to lower LDL-cholesterol blood level. Only some statins are recommended in HIV-treated patients.

Insulin-resistance plays a major role in the occurrence of metabolic disturbances during HIV-infection.

Metabolic parameters and cardio-vascular risk factors are important elements because HIV-treated patients live longer.

### The expert group's recommendations are:

To anticipate occurrence of lipoatrophy in limiting the use of thymidinic NRTIs, notably stavudin when an alternative exists (AIa).

To change antiretroviral regimen if drug-related side effects occur for less toxic drugs combination (AIa).

Obtain public funding for corrective measures in disabling lipoatrophy.

To perform yearly lipid and glucose assessment in all patients. Oral glucose tolerance test (OGTT) and insulin blood level measurements should be done when

metabolic syndrome or raised blood sugar are present (BIII).

To organize multidisciplinary management of cardio vascular and tobacco use risk factors within the COREVIH program.

## OPPORTUNISTIC INFECTIONS AND TUMORS

### Highlights

Prophylaxis against pneumocystosis and even toxoplasmosis is essential in patients who have less than 200 CD4 lymphocytes count (or less than 15% CD4/CD8 ratio) (AI).

Immune response inflammatory syndrome (IRIS) should be suspected when atypical clinical symptoms occur following treatment initiation in severely immuno compromised patients (AII).

IRIS may be anticipated by diagnosis of latent opportunistic infection (OI) in severely immuno compromised patients. An interval of a few weeks is often justified between treatment of OI (for OI with the greatest risk of IRIS) and the start of antiretroviral treatments (BIII).

Drug interactions are of particular concern with antituberculosis /anti fungal drugs and anti retroviral therapy (AII).

Cognitive dysfunction should be considered not only when symptoms are very evident but also in patients presenting with difficulties in organizing their daily lives, memory problems and/or in patients of over 50 years and/or those with unexplained first line treatment failure(BII).

In patients who are not severely immuno-compromised, neoplasia management is similar to that in uninfected individuals (BIII). Drugs interactions with antiretrovirals, addition of treatment toxicities and prophylaxis against OI should be anticipated (BII).

High frequency of lung and ENT neoplasia in patients living with HIV should prompt the physician to encourage the patient to stop smoking. This may be undertaken (frequently) in collaboration with specialized anti-smoking centre programs (BII).

### The expert group's recommendations are:

Cancer screening should be more systematic (A)

Routinely perform annual PAP smears in HIV-infected women (A). Colposcopically

guided biopsy should be systematic for all abnormal PAP results.

Anal PAP tests in men who have sex with men, in women with prior cervical cytological lesions or prior cervical cancer and in any patients having been treated for papilloma virus infection. Anal examination must be performed if cytological lesions are evidenced.

Screening several times a year for liver carcinoma in cirrhotic and co-infected HCV or HBV patients.

## NON-B SUBTYPE INFECTIONS (M GROUP), GROUP O AND HIV-2 INFECTIONS

### Highlights

#### **Non-B Subtype Group M**

Frequency of non-B subtype Group M viruses is increased and represents 47.8% of newly diagnosed HIV-infections between 2003 and 2005. Of these, about half are similar to the CRF02-AG form (circulating form in West Africa).

Patients with subtype D VIH-1 infections seem to progress more rapidly to death.

Non-B subtype Group M viruses are susceptible *in vitro* to all commonly used antiretroviral classes including fusion inhibitors.

Non-B subtype Group M viruses are similar to B subtype regarding treatment efficacy.

#### **HIV-1 Group O Viruses**

They are infrequent (0.2% of newly diagnosed infection between 2003 and 2005) and identified mainly in patients or partners who come from Cameroon.

Most of the approved tests are unable to determine group O VIH-1 viral load. Physicians should be consider group O virus when viral load is undetectable in naive patients or when there is discordance between immune status and viral load.

They are naturally resistant to NNRTIs.

Therapeutic guidelines are similar for HIV-1 Group O and B subtype viruses

#### **HIV-2 Infection**

Account for 1.9% of newly infected diagnoses between 2003 and 2005 (predominantly in patients who come from West Africa).

Disease progression is slower than in HIV-1 infection. Sexual and mother-to-



child transmission appears lower.

Only specific tests can detect viral HIV-2 load. Specific diagnostic testing is available in some specialised centre, notably through the ANRS CO5-VIH-2 cohort study. Less than 50% of patients have detectable viral load (> 100 copies/ml) with a median of 1000 copies/ml.

HIV-2 infection cannot be treated with NNRTIs and fusion inhibitors because of natural resistance to these classes. Susceptibilities to amprénavir, tipranavir and atazanavir also seem to be reduced.

The CD4 lymphocytes count increased more slowly in HIV-2 than in HIV-1-treated patients

**The expert group's recommendations are:**

**For HIV-1 non B subtypes (M group)**

To determine VIH-1group M subtype using genotypic resistance testing (AIII).

To monitor subtype D infected-patients very closely, as the evolution profile is very rapid (AII).

To treat subtype non-B infected-patients according to the recommendations for patients presenting with B sub-type infection (AI).

To assess therapeutic response for subtype B infected patients in clinical trials (BIII).

**For VIH-1 Group O infection**

Identify VIH-1 group O virus using serotypic methods when immune and viral status are discordant (low CD4 lymphocytes count and low or undetectable viral load in naive patients). This is particularly important in patients who come from Cameroon (AIIa).

Do not treat VIH-1 Group O infection with NNRTIs (AIa).

**For HIV-2 infection**

In asymptomatic naive patients, assess viral load every six months if undetectable at the last test and every three months if detectable (AIII).

Consider antiretroviral therapy when CD4 lymphocytes count approaches  $350/\text{mm}^3$  notably if the viral load is over 1000 copies/ml. Immune response could be lower (AIII).

Do not treat patients with VIH-1 Group O infection with NNRTIs and enfuvirtid (AIa). Use fosamprenavir, atazanavir and tipranavir with caution (possible decreased of susceptibility to these compounds) (BIIIb).

## IMMUNOTHERAPY

### Highlights

The two goals of immunotherapy are:

- to improve non specific immune response
- To increase HIV -specific immune response

Potential advantages of non specific immunotherapy (IL-2, pegylated alpha interferon) could result in antiretroviral treatment interruptions or simplification strategies. These strategies are still at the clinical research stage.

Studies are ongoing for specific immunotherapy using several vaccine vectors

### The expert group's recommendations are:

A close follow up of IL-2 treated-patients to assess medium and long-term tolerance

## POST EXPOSURE PROPHYLAXIS

### Highlights

Antiretroviral post exposure prophylaxis (PEP) is effective if treatment is administered early and adapted to the resistant mutations profile of the source-patient virus. However, failures have been reported.

Prevention and care management of occupational post exposure are well structured with encouraging results. However HIV-infected patients and their partners as well as the general population are not aware of the availability of PEP in most cases.

### The expert group's recommendations are:

To limit initiation of antiretroviral post exposure prophylaxis to documented HIV risk exposures (BIII).

To actively determine the HIV status of the source-person through rapid diagnostic testing (BIII).

To make available 2 or 3 days pack-treatment in the emergency room so that antiretroviral therapy may be offered as early as possible (BIII).

To refer patients seen initially by a non experienced clinician (CIII) to an HIV-care specialist to reevaluate the PEP indication after 3 or 4 days.

To treat with a PI/r + 2 NRTIs regimen for 28 days (BIII). Genotypic resistance testing should be performed if the source patient is HIV-infected with a detectable viral load in order to adjust therapy in exposed patients (BIII).

To follow up testing and care for 4 months in treated patients and 3 months in non-treated patients (AIII). Risk exposure for HBV, HCV and STDs should be also evaluated.

The COREVIH should assess and evaluate PEP intervention methods (CIII).

## HEALTH CARE MANAGEMENT

### HIV SCREENING

#### Highlights

HIV testing and counseling are key elements in prevention strategies: prevention messages can be delivered directly to the patient and patients with HIV infection can be referred directly to the specialist for advice. Screening should be more easily available.

#### The experts group's recommendations are:

Highlighting possibilities of HIV screening outside of free and anonymous testing clinics (CDAG). It is suggested that the National Aids Council (CNS) should lead a forum on improving HIV screening provisions.

Health Care professionals working in specific settings for at-risk populations such as recent immigrants and foreigners in precarious situation, should be encouraged to propose systematic HIV testing as part of a general free health screening package (permanence d'accès aux soins de santé, PASS).

Prison health care services should ensure good clinical practice in HIV testing and improve detainees access to screening.

### PREVENTION AND HEALTH EDUCATION

#### Highlights

Despite an improved recognition of the value of educational support and counseling in hospitals and day care centers, the organizational infrastructure is insufficiently developed and remains complex, particularly for out-patients. Additional money may be necessary.

#### The experts group's recommendations are:

Formalisation of educational support and counselling, including prevention counselling, within hospitals concerned with the care of HIV-infected people.

To offer health care professionals who wish to work in this area, training in health education.

To be permanently vigilant about prevention and health care policy in prisons.

## **NEW GOVERNANCE OF PUBLIC HOSPITALS**

### **The expert group's recommendations are:**

The setting up of two working groups:

The first group to focus on the costing of medical activity (T2A). This is important in order to ensure that the appropriate evaluations for standardized hospital stay cost (GHS) are made in the HIV/AIDS sector and that the specificities of HIV care are taken into account in the clinical coding (CCAM) and budgeting.

The second group to work on the means necessary to ensure good practice in HIV free and anonymous testing clinics and Regional HIV Coordination Groups (COREVIH).

## **POST OPERATIVE CARE AND REHABILITATION CENTERS**

### **The expert group's recommendations are:**

That units which admit young HIV infected patients suffering from major complications should be clearly identified.

That evaluation of needs at the regional level be carried out, taking into account the regional profile of the epidemic. This topic must be part of the Regional Health Care Plan (SROS).

That work should be done to get accurate knowledge of the volume and cost of the activity in Post-Operative and Rehabilitation Units (SSR).

That consideration be given to care after Post-Operative Rehabilitation.

That Regional HIV Coordination Groups should seek close working relationships with surrounding care structures and home care services.

## REGIONAL HIV COORDINATION GROUP

### The Expert Group's recommendations are

That Regional HIV Coordination Groups should be active in

- o Harmonising the care on offer in hospitals as well as in the community.
- o Setting up networks between all interested parties including Patients' Support Groups and health care system users.
- o Training doctors working outside hospitals on providing care for HIV infected patients.
- o Setting up research work and joint projects with doctors who work outside of hospitals.

## SOCIAL AND LEGAL ASPECTS

### The expert group's recommendations are:

#### For Immigrants and foreigners

- o That the free health care settings for at-risk groups (PASS) are better publicised in order to improve access to care and screening, including HIV testing, and help these persons to access to health insurance.
- o The *Guide to Care for Migrants* and others in socio-economic difficulties should be more widely available in order to publicise health care rights and facilitate access.
- o Legislation concerning ill non-French citizens should be fully respected. Training should be provided for social workers and administrators of the Health Insurance Scheme.

#### For Prisoners

- o Health care workers in detention centers should be informed on the legislation pertaining to health care of prisoners in order to improve the application of the Law lightening or suspending sentences for medical reasons.
- o Prisoners should be informed about the schemes lightening or suspending sentences for medical reasons.
- o A forum should be set up to consider medical reports dealing with lightening or suspending sentences for medical reasons.
- o To facilitate the creation of places in care facilities for HIV-infected people leaving prison.
- o To ask the National Aids Council (CNS) to draw a picture of the situation regarding screening and care of HIV infected people in prisons.