

**Recommended Principles of Antiretroviral Therapy
in HIV Disease**

**Scientific Committee on AIDS
co-sponsored by the Hong Kong Advisory Council on AIDS
and
the Centre for Health Protection,
Department of Health**

January 2005

About the Scientific Committee on AIDS (SCA)

The Scientific Committee on AIDS (SCA) was renamed from the former Scientific Working Group on AIDS. Its terms of reference and membership are as follows:

SCA has the following terms of reference :

- (a) to advise on the effective surveillance of HIV/AIDS, and the monitoring of the situation as it relates to Hong Kong;
- (b) to advise on the development of effective clinical and public health programmes on HIV/AIDS in Hong Kong;
- (c) to establish rationale and develop principles on the effective prevention, treatment and control of HIV infection in Hong Kong;
- (d) to promote the development of research agenda on HIV/AIDS and its related areas in Hong Kong; and
- (e) to promote regional and international collaboration of research activities in HIV/AIDS. (Note : new item proposed by SCA members)

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Preamble

In 1996, protease inhibitor became available in Hong Kong. Added to conventional nucleoside therapy, it provided potency and subsequently durability in the treatment of HIV infection. In line with experience abroad, mortality of HIV infected patients has decreased since then.

In 1996 and 1998, the Scientific Committee on AIDS (SCA) published its consensus statements on antiretroviral therapy, providing guidance to the local use of antiretrovirals.

With the rapid advancement of HIV medicine, certain principles of antiretroviral use have evolved. Hence, the SCA sees the need to define such principles for the local medical practitioners, having examined the availability of antiretroviral treatment, ancillary professional support, laboratory services as well as expertise in HIV disease management. Comments were also sought from the medical profession.

As such, the SCA views these principles as attainable and should be adhered to for the maximal benefit of patients. They effectively serve as the basis of the local standard of care.

Recommended principles

I. Highly active antiretroviral therapy (HAART) with potent and durable viral suppression to undetectable levels is the preferred therapy under most clinical circumstances.

1. For practical purposes, HAART may be defined as therapy which is potent enough to suppress HIV viraemia to undetectable levels, as measured by the most sensitive assay available, and which is durable in its virologic effect. Operationally defined as such, HAART implies the need of viral load for monitoring of efficacy.¹ Failure of full virologic suppression or rebound from undetectability calls for immediate review of the regimen.

2. HAART conventionally includes three or more drugs from at least two classes. Currently, there are three classes of antiretrovirals available in Hong Kong, the nucleoside reverse transcriptase inhibitor (including the nucleotide, tenofovir disoproxil fumarate), non-nucleoside reverse transcriptase inhibitor, and protease inhibitor.

3. However, as long as there is full and durable suppression of viral load, any regimen should be regarded as HAART. On the other hand, known suboptimal regimens, e.g. monotherapy, double nucleoside, or certain triple nucleoside combinations are not HAART and are contraindicated in HIV disease.

4. The goal of potent and durable viral suppression is paramount whether the treatment is the initial or subsequent regimens. A failing regimen generally requires at least two, and preferably three new drugs without cross resistance in a subsequent regimen to achieve this goal. Thus, adding or substituting only one new medication is contraindicated.

5. In certain circumstances it is difficult to concoct a regimen to achieve full viral suppression. These include multiple drug resistance, intolerance and multiple allergy to therapy. Nevertheless, limited viral suppression may still confer clinical benefit to the patient.² This phenomenon extends to prophylaxis against mother-to-child transmission where incomplete viral suppression by monotherapy reduces risk, although the goal of treatment should still be full suppression. In the case of post-exposure prophylaxis, viral suppression is not a

factor, and use of lesser drug regimens, e.g. double nucleosides, may be reasonable.

II. The initiation of antiretroviral therapy is a carefully meditated decision following a thorough medical evaluation and informed discussion with the patient.

6. Most authorities agree that symptomatic HIV infection, including AIDS-defining conditions and category 'B' symptoms warrant antiretroviral treatment.³ In primary HIV infection, there are also theoretical advantages of immediate treatment which are being evaluated in clinical trials.

7. In chronic, asymptomatic HIV infection, a low CD4 count below 200/ul is a widely accepted threshold for initiation of treatment.^{4,5,6} Nevertheless, in those with higher CD4 counts, the decision to initiate treatment should be a composite evaluation of the following factors:

- The level and trend of CD4 count – A marginal and falling CD4 count favours treatment
- The level of viral load – a high level in company with a marginal CD4 count favours treatment.

8. In all events, the patient's willingness to initiate and adhere to treatment is important.⁷ This should be based on his full comprehension of the rationale of treatment and its requirements. Specifically, he should understand

- the need of strict adherence and regular medical followup,
- the adverse effects and immune reconstitution associated with treatment, their implications and management, and
- the antiretroviral options available to him.

III. The design of a regimen should take into consideration factors related to the patient as well as the virus, with long term disease control as a major goal.

9. As the availability of antiretrovirals expands, the number of possible combinations multiplies, many of which qualify as HAART because of its virologic potency and durability as shown in clinical trials. However, all regimens do not perform equally for a patient. Furthermore, antiretroviral therapy is long term and potentially carries serious adverse effects. It is therefore imperative

that a regimen be individualised, after assessment of the following:

- possibility of unfavourable drug interactions,
- host factors that may hinder adherence, e.g. irregular working hours, depression, gastrointestinal disturbance, etc,
- viral factors that will suggest resistance, e.g. acquisition of HIV from a partner on treatment, and
- underlying risk factors or disease that will predispose to adverse effects of treatment, e.g. cardiovascular risk factors, metabolic syndrome, diarrhoea, etc.

10. The regimen itself is then optimised in frequency of administration, convenience and pill burden, before it is recommended to the patient.

11. This process is done to facilitate the design of a regimen and not to exclude certain patients from treatment. Assessment should be repeated during subsequent followup, with a view to timely adjustment to achieve long term control of disease.

IV. The offer of antiretroviral therapy is not dependent on predicted adherence. Anticipated difficulties in adhering to a regimen are proactively and empathically managed by appropriate selection of antiretrovirals, intensive counselling and disease monitoring, and correction of factors contributing to non-adherence.

12. There can be no overstating the importance of adherence in the successful use of HAART.⁸ Certain lifestyle factors are conventionally believed to be associated with non-adherence, most notable of which are substance use and commercial sex work. However, data supporting such associations are conflicting and their predictability of nonadherence is crude.^{9,10} To the contrary, it has been repeatedly shown that doctors' prediction of adherence is poor.¹¹

13. Recommendation for antiretroviral therapy should therefore be based solely on medical considerations. Although patient assessment includes that of factors contributing to nonadherence, the objective is to proactively correct these factors before and during antiretroviral use.¹² Depending on circumstances, it may be appropriate to intensify monitoring of adherence¹³ and disease, and institute preventive measures against adverse effects. Antiretroviral should be selected in ways conducive to long term adherence

which is to be actively monitored in all subsequent clinical encounters. Regardless, it is unacceptable to withhold treatment or prescribe suboptimal therapy because of expected noncompliance.¹⁴

V. Highly active antiretroviral treatment is but one of a whole array of medical therapies of HIV disease, the other components being effective infection prophylaxis, nutritional therapy, and immunisation.

14. The success of HAART overshadows other interventions in HIV disease that have shown proven clinical benefit. These include but are not limited to correction of anaemia, appropriate prophylaxis against opportunistic infections, nutritional therapy, and certain behavioural modifications that avoid contact with pathogens.¹⁵ Although treatment of latent tuberculosis probably does not prolong survival, the reduction in morbidity also justifies its use in HIV infected patients.¹⁶ Where appropriate, all these measures should be combined with HAART.

15. Immunisation is available against infections that share similar routes of infection, e.g. hepatitis B, and against infections that may opportunistically infect HIV-positive patients, e.g. pneumococcus. They should be considered in HIV infected patients.

VI. Novel antiretroviral therapy should be used only in a clinical trial setting where the patient understands the rationale and design of the trial, his potential gains from enrolment, possible adverse effects, and his right to withdraw at any point of time.

16. The rapid advancement of HIV medicine has witnessed unexpected drug interactions¹⁷ and reversal of recommendations.^{18,19} The lesson of caution is thus obvious in the use of novel combinations and novel drugs. A properly conducted clinical trial setting is most appropriate should such therapy be contemplated.

17. Use of novel agents or novel use of available agents is based on potential gains over established therapy. This situation is exemplified by the occurrence in some patients of multiple drug resistance where there is no standard salvage therapy. In a clinical trial setting, the overriding principle is

that a patient should only enrol after fully understanding its implications – especially the potential benefits to the patient and potential adverse effects with new treatment. Such studies should be administered according to the Declaration of Helsinki²⁰ and after proper evaluation of their ethical implications. Mechanisms of data monitoring and its regular review should be in place, detailed records should be kept, and informed consent be properly obtained. Should new relevant data or opinions emerge in the course of a study, they should be made known to the patients as soon as possible, even if this encourages them to withdraw from the study.

VII. HIV infection is not only a multi-organ disease but beset with enormous social implications. It can be successfully managed only by a multispecialty and multidisciplinary approach, with sensitivity and empathy.

18. HIV infection transcends organ systems and requires management by a multispecialty effort. Experts in antiretroviral therapy should collaborate with specialists of other disciplines, including ophthalmologists, surgeons, neurologists, psychiatrists, gynaecologists, dermatologists, paediatricians and primary care internists. Assistance of other professionals like medical social workers, counsellors, nutritionists and occupational therapists is also essential to a holistic, client-centred approach.

19. Intangible barriers to effective treatment exist in our society in the form of social marginalisation, although attempts are ongoing to eradicate all forms of discrimination against HIV-infected patients.²¹ Until then, the physician should be sensitive to such dynamics and be empathic in rendering care. Issues such as confidentiality, unprejudiced medical management, equitable access to care, and partner notification are particularly relevant.

VIII. Long term antiretroviral therapy should be prescribed only by physicians competent in the management of HIV disease, and in settings organised for optimal care.

20. The complexity of antiretroviral treatment, the lifelong commitment of patients to such therapy, and the unforgiving nature of drug resistance mandate prescription only by competent physicians. Currently, the high cost of medications practically limits prescription privileges to physicians of designated

HIV clinics in Hong Kong. However, as availability improves and cost decreases, there is a risk of inappropriate use and emergence of resistance, in a scenario reminiscent of antibiotics.

21. The SCA supports attempts to define qualities of practitioners required for appropriate prescription of antiretrovirals for the long term management of HIV disease. Such attempts should take into account the knowledge base of the physician, his experience and record of care of HIV patients, and evidence of continuing medical education.

22. It is also important that antiretrovirals be used in a setting where there is adequate laboratory support, especially in regard to the measurements of viral load and CD4 count, and testing of drug resistance. The indications for the latter are evolving and reference should be made to the best available evidence. There should also be access to consultations with other medical specialties and assistance by other professionals required for optimal care.

23. Short-term antiretroviral use is indicated in post-exposure prophylaxis and occasionally in prevention against mother-to-child transmission, sometimes on an urgent basis. Nevertheless, appropriate prescribing is still important in these circumstances. Therefore, the prescribing physician should either be qualified in antiretroviral use, or have access to expert advice. A peer-reviewed protocol should be available in settings where such use of antiretrovirals is conceivable, e.g. the Accident and Emergency Dept.

IX. While experience of antiretroviral use in overseas countries provides useful guidance, it is desirable that a local, systematized surveillance system be in place for monitoring of efficacy and unexpected adverse effects.

24. Most pre-licensure data on antiretrovirals were obtained in developed countries from studies on ethnic groups other than Chinese. Experience has shown that ethnicity may play a role in the incidence and pattern of adverse effects,^{22,23} as well as the very immunologic profile.²⁴ Local viral factors such as primary resistance may also be relevant. In addition, postmarketing surveillance has uncovered adverse effects never encountered before licensure.²⁵

25. It is thus a matter of principle that surveillance for adverse effects and antiviral efficacy be carried out despite drug licensure locally or abroad. It is also desirable that such collection of data be done in a systematic manner.

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