

**2002 QUINQUENNIAL REVIEW OF
THE NATIONAL CENTRE IN HIV
EPIDEMIOLOGY AND CLINICAL RESEARCH**

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7.1 SUMMARY AND RECOMMENDATIONS

7.1.1 Summary

In the five years since the last review, the National Centre in HIV Epidemiology and Clinical Research has continued to raise its already high national and international profile in clinical research and epidemiology. The following are among its achievements:

- ◆ a continuing lead role in the pathological and therapeutic aspects of primary HIV infection, with a recent award from the US National Institutes of Health of US\$3.67 million over five years
- ◆ a pivotal role in the development of anti-retroviral therapies and their evaluation in national and multinational trial networks, substantially influencing the clinical management of HIV/AIDS in Australia and internationally. The Centre has shown international leadership in a number of areas but particularly in the movement of the investigation of the therapeutic effects of interleukin-2 from early exploratory studies to two large international phase III trials
- ◆ studies of the clinical, pathological and therapeutic aspects of the metabolic toxicities associated with anti-retroviral drugs
- ◆ the establishment of a national HIV surveillance system, which is recognised nationally and internationally as a key component of the Australian response to HIV/AIDS, and the initiation of national surveillance for hepatitis C infection
- ◆ studies of the risks for HIV and hepatitis C infection in Australia and modelling studies, both of which have guided the national prevention response.

In addition, the Centre is the lead site for a national consortium that was successful in gaining A\$27 million from the National Institutes of Health to develop and clinically test a prophylactic HIV vaccine based on a novel approach developed in Australia.

The Centre's publication record is also impressive. It has published nearly 600 peer-reviewed articles (some 295 in the last five years) and 212 non-peer reviewed articles. At least 130 of the 295 peer-reviewed articles in the last five years appeared in journals with an impact factor of five or greater.

Internal and external management of the Centre

Internally, a new management structure was adopted early in 2002, with an executive and six programs of research each having a program head. This structure has given greater responsibility to a group of younger, talented researchers and clarifies their roles within the Centre. But a third tier of management needs to be created, especially in the case of the Therapeutic and Vaccine Research Program, which has 21 full-time-equivalent staff.

Externally, the Centre is advised by a Scientific Advisory Committee, which is large and allows for stakeholder input as well as scientific advice. As a result, the Committee has not achieved all that the Centre staff had hoped. Additional mechanisms may need to be explored

to expand the contribution of external expertise while not diminishing the input of stakeholders, particularly those from the community sector.

Funding

Since the last review, the Centre has attracted substantial funding from new sources, most notably the National Institutes of Health. The total annual award income in 1997 was A\$4.77 million; it is now \$11.7 million with a projected additional \$20 million income from National Institutes of Health support during the next five years. However, the core funding to support surveillance and infrastructure costs has been eroded because of a lack of adjustment for inflationary costs such as staff pay awards. 'Mainstreaming' is not particularly relevant for a Centre whose core functions—such as surveillance and maintenance of the clinical trials network—are not funded by 'mainstream' research bodies. The model of funding these functions, as an integral part of the Centre, could be considered a mainstream model.

The Therapeutic and Vaccine Research Program

The Therapeutic and Vaccine Research Program is outstanding. It has over 30 clinical trials in progress or to be started in Australia and through the HIVNAT collaboration in Thailand. It is one of the leading clinical trial centres in the world. In the last year, 1200 patients—some 15 per cent of people known to be living with HIV infection in Australia—were in clinical trials at 40 sites. This is a remarkable achievement. The research group was among the first in the world to characterise the lipodystrophy syndrome.

The pharmacology of antiretroviral drugs is an important area of developing research. The Centre wishes to begin a program in this area but has yet to develop or identify 'home-grown' pharmacological expertise.

The Centre is the lead site of a national consortium that was successful in gaining A\$27 million from the National Institutes of Health to develop and clinically test a prophylactic HIV vaccine.

The HIV Epidemiology and Prevention Program

The Centre is continuing its research into men who have sex with men, studying behavioural and biological risk factors in collaboration with the National Centre in HIV Social Research. Internationally recognised studies have been done on HIV-related cancers because of the ability to link the national HIV database with the cancer registry. This link is not available in many other countries. The future program of research will also include a phase III vaccine preparedness study in men who have sex with men and screening for a wide range of infections, a randomised controlled trial in non-occupationally HIV-exposed people, and continuation of the non-progressors cohort, which is an important resource for basic scientists to identify protective viral and host factors.

The Viral Hepatitis Program

The Viral Hepatitis Program includes surveillance, risk factor and long-term sequelae studies of patients infected with hepatitis B and hepatitis C. The Centre will extend its expertise in clinical trials to the assessment of treatments for blood-borne virus infection. This will be done in collaboration with the Australian Liver Association and other stakeholders through

the recently established Viral Hepatitis Working Group. There are plans to study the natural history and effects of treatment on patients with newly acquired hepatitis C infection. It is important that clinical trials in hepatitis C–infected injecting drug users be conducted in collaboration with providers of their long-term care.

The Primary HIV Infection Program

The Centre will continue its research in the primary infection area, for which it has already earned an international reputation and has recently been awarded funding from the National Institutes of Health of US\$3.67 million over five years for a collaborative project with a group at Harvard University.

The Biostatistics and Databases Program

The primary role of the Biostatistics and Databases Program is to support developments across the breadth of the Centre's work: approximately 75 per cent of the Program's resources are dedicated to this. The Australian HIV Observational Database has been established for two years and is contributing data to large international cohort studies of the cardiovascular risks of therapy and the effects of salvage therapy. This Program illustrates the significance of a biostatistical infrastructure investment attracting additional funding in the national and international contexts.

The Laboratory Program

The Laboratory Program has two functions. It provides services and support for the other programs by being a repository for samples and is thus an important national resource. It is also responsible for transitional and pathogenesis research. New assays are validated and then moved into routine use. The pathogenesis research is focusing on immunological changes in primary infection, which might determine long-term outcomes such as immune escape, the effect of therapy, and novel resistance mutations. The Laboratory Program was involved in the establishment of, and now supports and audits, the laboratories in Thailand as part of the HIVNAT collaboration.

Surveillance

Surveillance is a core function of the Centre. Directions for future development include newly acquired infections in HIV, expansion of activities in hepatitis B and C, and development of sexually transmissible infection surveillance beyond the current passive surveillance to National STI Surveillance Strategy under the auspices of the Communicable Diseases Network Australia. The annual surveillance report is a key output. The Centre has been given a small amount of additional core funding for hepatitis B and C surveillance, but expansion into the area of STIs, with work needed to improve the quality of data, will require additional core funding.

Role in the Asia–Pacific region

The clinical trial effort in Thailand is now well established and the Centre has a leading role in the HIVNAT collaboration. Thailand is already involved in several vaccine trials. Setting up vaccine trials in other developing countries will require long and intensive preparation.

Support from AusAID should be sought for this important development work, and it may be necessary for the Centre to work with other groups in Australia who have a longer history of experience in developing countries.

Indigenous Australians' sexual health

The Centre's contribution to Indigenous Australians' sexual health comes largely through its support for the National Indigenous Australians' Sexual Health Strategy. The Centre has also provided technical support to the Tri-state Program in Central Australia. Although the Centre's contribution may not have been as extensive as envisaged by the previous Review Panel, it has made substantial contributions, in keeping with its expertise and recognising that substantial progress across the health care system may enable further contributions.

The relationship between the Centre and the University of New South Wales

The Centre is an off-campus centre of the University of New South Wales Faculty of Medicine; it uses its own funds to rent accommodation. Staff of the Centre carry a considerable graduate teaching burden. There are no directly funded tenured posts, but two to four computer and administrative staff are funded by the University. Academic career development within the University and the promotion of Centre staff, particularly the program heads carrying out clinical trial work, was of concern to the Review Panel. Discussions should begin between the Centre and the University to redefine their relationship, with input from other appropriate authorities. These discussions should take into account the long-term vision for the Centre.

The previous review

The Centre was last reviewed in 1997, and the reviewers made 26 recommendations (see Section 7.6 (Appendix C)). The current Review Panel assessed the Centre's performance in the light of these recommendations and was completely satisfied that, with four exceptions, the recommendations had been fully implemented. The four exceptions are:

- ◆ The Centre should continue and strengthen its work in relation to Indigenous people as one of its highest priorities. (recommendation 3)
- ◆ Health services research undertaken by the Centre should encompass cost-effectiveness studies and studies regarding compliance with prophylactic and therapeutic regimens. (part of recommendation 6)
- ◆ The expertise of the Centre should formally be brought to the attention of AusAID and ... AusAID [should] be encouraged to utilise the expertise available in the Centre. (recommendation 25)
- ◆ Discussion should be undertaken with AusAID during the current review of AusAID's Health Program to clearly delineate the relative expectations and responsibilities of AusAID and the Centre in relation to training and other assistance to countries in the Western Pacific and South East Asian regions. (recommendation 26)

These matters are discussed later in this report.

7.1.2 Recommendations

The following is recommended:

145. That a third level of management in the Centre be introduced.
146. That the Scientific Advisory Committee be streamlined, so that it provides the scientific guidance the Centre needs and that alternative mechanisms be explored for expanding the contribution of collaborators, stakeholders and other experts to the Centre's work.
147. That in the next five years the Centre receive core funding that takes into account annual inflationary costs and the Centre's expanding surveillance functions (see also recommendation 151).
148. That the Centre identify or develop national expertise in anti-retroviral pharmacology to support this area of research.
149. That the Centre conduct trials in hepatitis C-infected injecting drug users in collaboration with providers of their long-term care.
150. That the Centre explore, through further national and international collaboration, use of its unique repository of specimens on HIV-infected patients.
151. That the small amount of additional core funding for hepatitis C and B surveillance be extended for five years, taking into account annual inflationary costs. Expansion into the area of STIs, with improvements in the quality of data, will require additional core funding.
152. That support be sought from AusAID for expansion of the program in the Asia-Pacific region and preparation for the vaccine work. It may be necessary for the Centre to work with other groups in Australia who have a longer history of working experience in developing countries.
153. That the Centre continue to expand its work on Indigenous Australians' health, including hepatitis C, through its work with the Indigenous Australians' Sexual Health Committee and in collaboration with other research and health service provider organisations with expertise in Indigenous health.
154. That discussions begin between the Centre and the University of New South Wales to redefine their relationship, with input from other appropriate authorities. These discussions should take into account the long-term vision for the Centre.
155. That the Centre consider changing its name in the light of its current and future activities.

7.2 THE REVIEW PROCESS

The members of the Review Panel were:

Chair: Professor Ian VD Weller
Department of Sexually Transmitted Diseases
Royal Free and University College Medical School, London

Members: Professor Roel A Coutinho
Municipal Health Service
Amsterdam and Academic Medical Centre/University of Amsterdam

Dr Cathy Mead
National Public Health Partnership, Melbourne

Secretariat support was provided by Ms Deb Sullivan, Flinders Medical Centre, Bedford Park, South Australia.

Professor Peter McDonald, Chair of the Clinical Trials and Research Committee of the ANCAHRD was available to provide advice.

The Terms of Reference for the review are set out in Section 7.4 (Appendix A).

The Centre was required to make a written submission to the Review Panel in April 2002, in the format of an NHMRC Program Grant, detailing projects, achievements and future plans.

Three independent experts were asked to assess and rate the achievements, research plan and team, and cooperation based on the Centre's submission. The Centre was subsequently given the opportunity to reply to each assessor's report.

The Review Panel reviewed the following documents:

- ◆ the submission by the National Centre in HIV Epidemiology and Clinical Research (April 2002)
- ◆ annual reports from the Centre (1998 to 2001)
- ◆ the report of the third review of the National Centre (October 1997)
- ◆ the *Review of Australian HIV/AIDS Research* (August 1999)
- ◆ the *National Indigenous Australians' Sexual Health Strategy 1996–97 to 1998–99*
- ◆ the *National Hepatitis C Strategy 1999–2000 to 2003–04*
- ◆ the *Annual Surveillance Report 2001*.

Submissions were sought from stakeholders and interested parties. Written submissions were received from:

- ◆ the Victorian Department of Human Services

- ◆ the New South Wales Department of Health
- ◆ the Australian Federation of AIDS Organisations
- ◆ the Australian Hepatitis Council
- ◆ the University of New South Wales
- ◆ the Australian Liver Association of the Gastroenterological Society of Australia
- ◆ the National Drug and Alcohol Research Centre
- ◆ the Department of Clinical Immunology and Biochemical Genetics, Royal Perth Hospital
- ◆ the Australasian Society for HIV Medicine
- ◆ the US National Institutes of Health, Department of Health and Human Services
- ◆ the Australian Injecting and Illicit Drug Users League
- ◆ the National Drug Research Institute
- ◆ the Australian Red Cross Blood Service
- ◆ the Inter-governmental Committee on HIV/AIDS, Hepatitis C and Related Diseases
- ◆ Queensland Health
- ◆ Queensland Health's Community Services Program, the Prince Charles Hospital Health Service District Sexual Health and AIDS Service
- ◆ the Clinical Trials Group, UK Medical Research Council
- ◆ the US Department of Veterans' Affairs Community Programs for Clinical Research on AIDS
- ◆ the South Australian Department of Human Services
- ◆ People Living with HIV/AIDS (NSW) Inc.
- ◆ the Burnet Institute for Medical Research and Public Health Ltd
- ◆ the National Association of People Living with HIV/AIDS
- ◆ the Indigenous Australians' Sexual Health Committee, ANCAHRD
- ◆ the Office for Aboriginal and Torres Strait Islander Health.

The Review Panel met with the executive team and program heads of the National Centre in HIV Epidemiology and Clinical Research on Monday 2 June 2002 and continued its deliberations on Tuesday 3 June.

An oral report of the Panel's findings and provisional recommendations was presented by the Chair, Professor Ian Weller, to the Strategy Research Review Team on 4 June 2002. The report was finalised following this meeting and submitted to the Review Team on 6 June 2002.

7.3 THE REVIEW PANEL'S FINDINGS IN DETAIL

7.3.1 Management of the Centre

Internal

The National Centre in HIV Epidemiology and Clinical Research has 70 full-time-equivalent staff (there were 38 in 1997) and 26 of these are academic staff (11 in 1997). Earlier this year the Centre's internal management was restructured into six programs, each with a program head, and a finance and administration unit (see Section 7.7 (Appendix D)).

All the program heads meet with the executive committee twice a month. The meetings cover research and administrative matters alternately. Each program has its own research meeting and there are several joint programs.

The revised structure has given greater responsibility to a group of younger, talented researchers and clarifies their roles as research program heads. The Centre is well aware of the need now for a third tier of management, particularly in the case of the Therapeutic and Vaccine Research Program, which is the largest program by far.

Recommendation 145

That a third level of management in the Centre be introduced.

External

Most of the recommendations of the previous review have been implemented, and a Scientific Advisory Committee has been established. However, this group is large and constituted in such a way as to provide stakeholder input as well as high-level scientific advice in the development of the Centre's programs and initiatives. As a result, it has not achieved all that the Centre staff had hoped.

Additional mechanisms may need to be explored to expand the contribution of external expertise while not diminishing the input of stakeholders, particularly those from the community sector. The possibility of holding annual scientific forums with collaborators, working group leaders, community representatives, and some international experts should be explored. If such forums were held regularly the Scientific Advisory Committee could be streamlined to provide the scientific guidance and critique that the Centre needs.

Alignment of IGCAHRD as a subcommittee of the Communicable Diseases Network Australia, which in turn reports to the National Public Health Partnership, provides an opportunity for the surveillance activities to be better integrated with broader communicable diseases surveillance and control functions.

Recommendation 146

That the Scientific Advisory Committee be streamlined, so that it provides the scientific guidance the Centre needs and that alternative mechanisms be explored for expanding the contribution of collaborators, stakeholders and other experts to the Centre's work.

7.3.2 Funding

Since the last review, the Centre has attracted substantial funding from new sources, most notably the US National Institutes of Health. However, the core funding (A\$3.7 million in 2002, compared with \$3.34 million in 1997) is not keeping pace with costs—for example, staff costs and the cost of expansion into new areas of infrastructure. This could over time erode the Centre's capacity to compete as successfully as it does for external funding, and it will diminish the quality of core functions such as surveillance, clinical trials infrastructure and administration. The Centre has only recently become eligible to apply for NHMRC funding, and it can be expected that its success in this area will grow, given its track record in attracting external funds. The Centre's dependence on private sector funds, noted in the last review, has shifted substantially to international public sector funds.

Models for maintaining and expanding the funding of the Centre's core infrastructure were discussed. The model of 'deblocking' centres previously block-funded under the NHMRC is not appropriate for this Centre because the core funding supports infrastructure programs such as surveillance and the development and maintenance of the clinical trials network, which are unlikely to be funded in a competitive system based on funding of investigator-initiated research. Other models of funding need to be explored. In addition, discussion of 'mainstreaming' is not particularly relevant for a Centre whose core functions are not funded by 'mainstream' research funding bodies. The model of funding surveillance as an integral part of a national research centre could be considered a mainstream model.

The Centre's competitiveness internationally in attracting National Institutes of Health funds, amounting to US\$20 million over five years, illustrates the substantial return on the investment through core funding.

Support for the Centre's expanding surveillance functions has been minimal and this needs to be remedied if the surveillance strategies for hepatitis C and B and STIs are to be implemented.

Recommendation 147

That in the next five years the Centre receive core funding that takes into account annual inflationary costs and the Centre's expanding surveillance functions (see also recommendation 151).

7.3.3 The Therapeutic and Vaccine Research Program

Therapeutic research

The Therapeutic and Vaccine Research Program is the Centre's largest research program, with 21 full-time-equivalent staff (11 academic) and 11 external staff research nurses. The Program has a large number of project teams with cross-program membership (for example, the Biostatistics and Laboratory Programs) and these teams involve external investigators.

The Program's objectives are to evaluate new treatments, new treatment strategies and candidate HIV vaccines and to conduct other studies of HIV's natural history and treatment-related side-effects. The Program has over 30 clinical trials in progress or to be started in Australia and through the HIVNAT collaboration in Thailand. There is a balanced mix of investigator-initiated studies, multinational studies and pharmaceutically driven studies.

Through this Program the Centre has continued to raise its profile as one of the leading clinical trial centres in the world. It not only participates in pivotal international studies but also has shown great leadership in moving agents such as interleukin-2 through early exploratory trials to phase III assessment in multinational studies involving thousands of patients.

Essential to the Program's success is the network of investigators in hospitals and general practice across Australia. In the last year 1200 patients (some 15 per cent of people known to be living with HIV infection in Australia) were in clinical trials at 40 sites, and Program staff had direct responsibility for the management of research protocols in other countries that have recruited 1500 patients. The Review Panel viewed this as a remarkable achievement.

The 1997 Review Panel recommended that health services research done by the Centre encompass cost-effectiveness studies. This research would require the Centre to provide relevant data to a health economist in Australia who was motivated to establish a research program in this area. This has not occurred.

Vaccine research

The Centre is the lead site of a national consortium that was successful in gaining A\$27 million funding from the National Institutes of Health to develop and clinically test a prophylactic HIV vaccine. It is one of only a small number of AIDS vaccine projects worldwide that have received National Institutes of Health funding. A consortium of Australian researchers has developed a prime and boost vaccine technique, and the Centre is leading the consortium in the clinical evaluation with a phase I/II proof-of-concept study to evaluate immunogenicity and safety. A more expanded phase II study will be conducted in Thailand, and a vaccine preparedness cohort and related infrastructure will be established in readiness for a definitive phase III efficacy study should the earlier phase studies prove sufficiently promising.

HIV-associated lipodystrophy

The Centre's research network was among the first in the world to characterise and report the lipodystrophy syndrome in 1998. It has since undertaken seminal studies to describe the syndrome's prevalence, incidence and biochemical aspects, as well as approaches to treatment and clinical management.

Pharmacology

An important area of developing research is in the pharmacology of anti-retroviral drugs. Metabolism of these drugs is complex, with substantial intra- and inter-patient variability in pharmacokinetics. There are also important drug-drug interactions that are yet to be fully elucidated. The Centre wishes to begin a program in this area but has yet to develop or identify 'home-grown' pharmacological expertise.

Recommendation 148

That the Centre identify or develop national expertise in anti-retroviral pharmacology to support this area of research.

7.3.4 The HIV Epidemiology and Prevention Program

At the global level the majority of HIV infections are heterosexually acquired, but in Australia about 80 per cent of infections occur among men who have sex with men. As a consequence, the Centre has concentrated its research efforts in epidemiology on this group, studying both behavioural and biological risk factors, often in collaboration with the National Centre in HIV Social Research. A new cohort of high-risk HIV-negative gay men has been established, and among recent seroconverters risk factors of infection have been identified; this has helped guide intervention campaigns among men who have sex with men in Australia. Additionally, an observational study of drug side-effects and compliance was established among people receiving post-exposure prophylaxis after non-occupational exposure to HIV. Internationally recognised studies have been done on HIV-related cancers because of the Centre's ability to link the national HIV database with the cancer registry. This link is not available in many other countries. A large non-progressors cohort has been established.

The Centre plans to continue its study of risk factors for recent infection. A Phase III vaccine preparedness study will be started, funded through the grant obtained from the National Institutes of Health. This study will enrol about 2000 men who have sex with men, from whom epidemiological information will be collected and blood stored. If funding is obtained, apart from HIV testing, testing will be carried out for other blood-borne and STIs, such as hepatitis C, HHV-8, *Chlamydia trachomatis* and gonorrhoea. For non-occupational exposure, a randomised controlled trial of a single drug, tenofovir, is under consideration. The linkage studies on HIV-related cancers will also continue, concentrating on long-term HIV-infected people. The non-progressors cohort will be expanded and will remain an important source for national and international in-depth virological and immunological laboratory studies, which will attempt to identify viral and host factor mechanisms for non-progression.

Collaboration with the National Centre in HIV Social Research

In both the Surveillance and the Epidemiology Programs of the Centre there is collaboration with the staff (particularly quantitative social scientists) of the National Centre in HIV Social Research, which is also part of the University of New South Wales but at a different location and in a different faculty. Such collaboration is considered essential for both parties; it should be maintained and, if possible, strengthened—for example, by joint appointments between the two Centres.

7.3.5 The Viral Hepatitis Program

In the past the Centre has used its HIV expertise to extend its activities to viral hepatitis B and C, concentrating on surveillance of these infections and studying risk factors and long-term sequelae. These studies have been important for better estimating the burden of these infections and have assisted in the development of public health programs for the prevention,

treatment and care of hepatitis B and C infection in Australia. Internationally recognised studies have been done on the natural history of chronic hepatitis C infection in both HIV-negative and HIV-positive people.

The Centre will use its knowledge and experience in HIV clinical trials to increase its contribution to therapeutic research into viral hepatitis. The studies will be done in close collaboration with the Australian Liver Association and other partners through the recently established Viral Hepatitis Working Group. This work will not only be undertaken with industry sponsorship but also by investigator-led grants. Risk factors for hepatitis C transmission will be studied in both injecting drug users and other groups. The Centre is involved in evaluating the effectiveness of medically supervised injecting and other harm-reduction programs aimed at preventing hepatitis C (and HIV) transmission. A prospective cohort of people with newly acquired hepatitis C infection will be established so that the natural history of primary infection and the effects of therapy can be studied. A grant application for this study has been submitted to the US National Institute of Drug Abuse. Long-term sequelae of hepatitis C infection will be studied using several approaches: a retrospective cohort study; meta-analysis of the literature; and the establishment of an observational database. Another research objective is to measure the quality of life in people with chronic hepatitis C infection.

The Viral Hepatitis Program has great promise, especially because of the Centre's experience with multicentre trials of HIV anti-retrovirals. Until now work has mainly involved trials among gay men, who are known to be highly compliant and in whom follow-up is good. Experience should be gained in setting up similar trials among the most important hepatitis C risk group—injecting drug users. Such studies can be done only in collaboration with the people who provide long-term care for injecting drug users.

Recommendation 149

That the Centre conduct trials in hepatitis C–infected injecting drug users in collaboration with providers of their long-term care.

7.3.6 The Primary HIV Infection Program

The Primary HIV Infection Program is another area where the Centre has been recognised as an international leader. Its success rests on its ability to identify early infection, using its national network of investigators; on-site, rapid laboratory testing; its laboratory support and research program; and the repository of stored material from patients. This is an example of the Centre's interdisciplinary strength. The future program aims to cover:

- ◆ the natural history of early immunological changes and their correlation with viral set-points and disease progression
- ◆ the effect of treatment—structured treatment interruptions and therapeutic vaccination—on these responses
- ◆ the transmission of drug-resistant viruses.

Just before this review the Centre was awarded National Institutes of Health support of US\$3.67 million over five years for components of this work to be carried out with Harvard University in the Acute Infection and Early Disease Research Program.

7.3.7 The Biostatistics and Databases Program

The primary role of the Biostatistics and Databases Program is to support developments across the breadth of the Centre's work: approximately 75 per cent of the Program's resources provide this support. Key directions for the future include modelling, supporting observational databases, methodology developments, and database support.

The Australian HIV Observational Database has been established for two years; the national clinical trial network of hospital and general practitioner sites enabled its establishment. In the absence of randomised clinical trials, observational databases are the next in line in the hierarchy of evidence for treatment effects. The Database is contributing to large international efforts. The Data Collection on Adverse events of Anti-HIV Drugs (DAD) study is a prospective study—initiated by the European Medicines Evaluation Agency in more than 19 000 HIV-infected patients—examining the possible association of anti-retroviral therapy and premature cardiovascular disease. The Performance of Lopinavir/Ritonavir as an Alternative Treatment Option (PLATO) study is a similar study, evaluating the effects of salvage therapy in patients whose treatment options are limited. The Centre plans to establish a hepatitis C observational database in Australia and an HIV observational database in Asia. The Program leader serves on the steering committee of the international cohort studies and provides statistical advice.

This Program illustrates the importance of a biostatistical infrastructure investment in attracting substantial additional funding in the national and international contexts.

7.3.8 The Laboratory Program

The Laboratory Program is based on the combined resources of the Centre, the laboratories at the St Vincent's Hospital campus, and the New South Wales State HIV Reference Laboratory. An excellent additional laboratory facility was incorporated in the Centre's organisation when space became available in the Garvan Institute and the new Program Head returned from postdoctoral studies in Oxford, UK.

Service and support for other programs

In the last five years the Program has accommodated an annual average of 1200 requests for cell storage, 2600 for serum or plasma storage, and over 400 for processing of other specimens involving lymphoid tissue, serum and cerebrospinal fluid for the other Centre programs. It also provides non-routine assays such as extended flow cytometry panels.

Transitional and pathogenesis research

Transitional and pathogenesis research is being carried out mainly in the context of natural history studies and clinical trials.

New assays for antiviral resistance, immunophenotyping and functional assays have been validated and then moved into routine or semi-routine use. Work of this kind will continue. Immunogenicity assays will be used in support of the prophylactic vaccine studies, and novel techniques such as the synthesis of MHC class II tetramers to study antigen-specific CD4+ T-cell responses are being developed in collaboration with the University of Oxford.

Pathogenesis research will be in the areas of primary infection, examining antigen-specific T-cell turnover; the time course of plasmacytoid dendritic cell depletion, its functional implications and the effect of therapy; the mechanisms and implications of immune escape; and novel resistance mutations outside the pol and protease genes.

A national resource

The repository of specimens is an important national resource. There is ample evidence of this in the repository's use by external investigators—for example, Martyn French (Perth), collaborating on the Initio substudy; Stephen Kent (Melbourne) and Rose French (Sydney), within the vaccine collaboration; Simon Mallal (Perth), working on the supply of primary infection sequences; Robert Oerlich (Melbourne), working on seroconverter samples for phylogenetic analysis; and Wayne Dyer and John Sullivan (Sydney Blood Bank) and Tony Cunningham and Nitkin Saksena (Westmead), working on long-term non-progressors.

Support for the HIVNAT program in Thailand

The Laboratory Program has overseen the establishment of a laboratory support program for the clinical trials and studies encompassed by the HIVNAT collaboration in Thailand and continues to audit laboratory standards. Encouragingly, this has led to a rolling-out of expertise, with Thai scientists upgrading other Thai laboratories.

Recommendation 150

That the Centre explore, through further national and international collaboration, use of its unique repository of specimens on HIV-infected patients.

7.3.9 Surveillance

The Surveillance Program, under the supervision of the Deputy Director, to a large extent occurs within other programs.

The Centre has substantial expertise in the development of surveillance under the Australian federal structure and the legal frameworks operating in the states and territories. The three areas of HIV/AIDS, hepatitis C and B, and STIs are in various stages of development, as shown in Section 7.8 (Appendix E).

Among the directions for future development are newly acquired HIV infections, expansion of surveillance activities in hepatitis C and B, and the development of national STI surveillance, beyond the current passive surveillance to a National STI Surveillance Strategy under the auspices of the Communicable Diseases Network Australia. The annual surveillance report is a key output from this Program.

Surveillance is one of the Centre's primary functions. Expansion into the area of STIs, with improvements in the quality of data, will at some point require additional core funding so that the developing National Strategy can be implemented. Some supplementation has been provided for hepatitis C and B; this needs to continue.

For STI surveillance, a close relationship with STI physicians and other parties will be required. This could be achieved through a model similar to the Viral Hepatitis Working Group.

Given the Centre's expertise in surveillance and the investment made in developing this capacity, there is scope for expansion of activities beyond the current areas. The Centre has already made a contribution, for example, to surveillance of Creutzfeldt–Jakob disease. Expansion to other infectious diseases would require greater integration between the Centre's surveillance activities and expertise and work being done under the auspices of the Communicable Diseases Network Australia.

The National Public Health Partnership has recently decided to streamline reporting arrangements and has designated the IGCAHRD as a subcommittee of the Communicable Diseases Network. The Partnership has also asked that IGCAHRD oversee development work on a national approach to STI control. It sees chlamydia as an initial priority for this work.

Recommendation 151

That the small amount of additional core funding for hepatitis C and B surveillance be extended for five years, taking into account annual inflationary costs. Expansion into the area of STIs, with improvements in the quality of data, will require additional core funding.

7.3.10 Work in the Asia–Pacific region

The Centre has played an important part in establishing in Bangkok a clinical trial centre that is now able to conduct HIV therapeutic trials of international standard. The experience gained could be used for future HIV vaccine trials, since this is a direction the Centre is pursuing. However, Thailand is involved in several vaccine trials (phases I, II and III) and there may be insufficient capacity to perform additional trials in that country, especially phase III efficacy trials. Setting up HIV vaccine trials in other (developing) countries in the region will require long and intensive preparation, both to establish the necessary infrastructure and to avoid tensions. Experience in Thailand, and in African countries, shows that vaccine trials are possible only if the medical professionals, politicians and communities involved support them. The Centre is therefore well advised to start the necessary preparations for HIV vaccine trials in developing countries in the region—not only for phase III trials but also for phases I and II. Support from AusAID should be sought for this infrastructure- and capacity-building work, and it may be necessary for the Centre to work with other groups in Australia with a longer history of experience in developing countries.

Recommendation 152

That support be sought from AusAID for expansion of the program in the Asia–Pacific region and preparation for the vaccine work. It may be necessary for the Centre to work with other groups in Australia who have a longer history of working experience in developing countries.

7.3.11 Indigenous Australians' sexual health

The previous review recommended that Indigenous Australians' sexual health become one of the Centre's highest priorities.

The Centre's contribution in this regard comes largely through its support for the National Indigenous Australians' Sexual Health Strategy. The Indigenous Australians' Sexual Health Committee is also represented in working groups, including the Scientific Advisory Committee and the Communicable Diseases Network Australia STI surveillance committee. In addition, the Centre has provided technical support to the Tri-state Program in Central Australia.

Areas of future work include improving surveillance, involvement of communities in all areas of the Centre's work and, in particular, developing contributions that reflect the Centre's expertise. This would involve working with urban communities and injecting drug users, in partnership with others, and involving communities and individuals in treatment trials. Further work on national STI surveillance could lead to expanded research capacity in relation to STIs relevant to Indigenous communities.

Although the Centre's contribution may not have been as extensive as envisaged in the recommendation of the 1997 review, it has contributed in keeping with its expertise and recognising that substantial progress across other areas of the health system may enable further contributions. Involvement of Indigenous people and communities in clinical trials, particularly hepatitis C trials, could become a significant contribution.

Recommendation 153

That the Centre continue to expand its work on Indigenous Australians' health, including hepatitis C, through its work with the Indigenous Australians' Sexual Health Committee and in collaboration with other research and health service provider organisations with expertise in Indigenous health.

7.3.12 University collaboration

The Centre is an off-campus centre of the University of New South Wales Faculty of Medicine; it uses its own funds to rent accommodation. In contrast, the University has provided a permanent home for the National Centre in HIV Social Research through the Faculty of Arts and Social Sciences. The University's submission to this review acknowledges the unique contribution the National Centre in HIV Epidemiology and Clinical Research is making and the value of its association with the University. Staff of the Centre carry a considerable graduate teaching burden and, in addition to masters courses, 27 higher degree students have completed their theses under the supervision of Centre staff. Further, there are no directly funded, tenured posts within the Centre. Two to four computer and administrative staff are funded from the return by the University Research Infrastructure Block Grant/Research Quantum.

Academic career development within the University and the promotion of Centre staff, particularly the program heads carrying out clinical trial work, was of concern to the Review Panel. This is important in terms of these people's national and international recognition. In addition, academics working in large clinical trials spend a large amount of time in

facilitatory and developmental work. A 'single experiment' can take several years. Production of a single publication represents considerable scientific endeavour, with an authorship that often hides the contribution of the 'main players'. As a result, the publication output of a clinical trial scientist cannot compete with that of other clinical and basic scientists.

These difficulties with the relationship between the Centre and the University should be taken into account in the long-term vision for the Centre.

Recommendation 154

That discussions begin between the Centre and the University of New South Wales to redefine their relationship, with input from other appropriate authorities. These discussions should take into account the long-term vision for the Centre.

7.3.13 Centre name

Recommendation 155

That the Centre consider changing its name in the light of its current and future activities.

7.4 APPENDIX A THE REVIEW PANEL'S TERMS OF REFERENCE

Following are the Terms of Reference for the Review Panel:

In the context of assessing the scientific quality and international competitiveness of research, each Discipline Specific Review Panel will review and make recommendations on:

Research goals and priorities

- ◆ The current strategic planning processes, goals and priorities and progress made towards meeting the stated goals/priorities;
- ◆ The relationship of current and projected research activities to the stated goals and priorities of the Centres and the extent to which they reflect, and can inform, emerging priorities;
- ◆ The extent to which the goals and activities reflect the needs of key stakeholders (ie Commonwealth and State/Territory policy makers, ANCAHRD, AFAO, Hepatitis C organisations, NAPWA, the medical and research communities (including ASHM), and Aboriginal people and Torres Strait Islanders);
- ◆ The contribution of each Centre's organisation and management structure to the attainment of the goals and its role in fostering interaction with each other and with ANCAHRD;
- ◆ To assess the effectiveness and appropriateness of Centre mechanisms for providing scientific guidance and accountability with respect to research objectives, including the Scientific Advisory Committees where relevant.
- ◆ Evaluate the cost-effectiveness, utility and efficiency of hepatitis C and STI surveillance as carried out by the NCHECR.

Research dissemination and exchange

- ◆ The nature, appropriateness and effectiveness of Centre mechanisms for disseminating research findings and information policy developments.
- ◆ The extent and value of the collaboration of the Centres with researchers in the HIV/AIDS, hepatitis C and related areas (eg Drug and Alcohol Research Centres) and the Centres' success in encouraging leading researchers to focus attention on HIV, hepatitis C and related research;
- ◆ The extent and value of Centres' relationships / collaborative arrangements with other key organisations, such as
 - centres funded under the Public Health Education and Research Program;
 - funding bodies;
 - government departments.
 - the host university; and
 - international bodies, such as UNAIDS, WHO and overseas universities/research centres.
- ◆ The extent and value of additional funding attracted by National Centres including:

- the extent to which this funding contributes to the Centre’s primary goals;
 - the value to Australia of such external funding; and
 - the capacity of existing Centres to attract and maintain external funding.
- ◆ The extent and value of the training opportunities provided by the Centres for researchers and those working in areas relevant to the Centres’ activities.

Other

- ◆ Other matters considered relevant or which emerge during the review.

7.5 APPENDIX B THE CENTRE'S TERMS OF REFERENCE

Following are the Terms of Reference for the National Centre in HIV Epidemiology and Clinical Research:

Research and surveillance

- ◆ To initiate, enhance, support and coordinate national surveillance for HIV/AIDS, blood-borne viruses and STDs in Australia in collaboration with State, Territory, Commonwealth and other relevant agencies.
- ◆ To initiate and carry out research into epidemiological and clinical aspects of HIV/AIDS, blood-borne viruses and STDs, including transmission, natural history and health services.
- ◆ To review, evaluate, co-ordinate, participate in and provide assistance for, clinical trials of therapeutic substances for the treatment of HIV/AIDS.
- ◆ To develop collaborative research related to the Centre's primary areas of activity internationally, particularly in the Asia-Pacific region.

Leadership and research resources

- ◆ To maintain close liaison and collaboration with the National Centre in HIV Virology Research, the National Centre in HIV Social Research, the National HIV Reference Laboratory and other collaborating centres including providing assistance in research design, development of data collection instruments, data processing and analysis and, to a limited extent, conducting research into natural history studies and the clinical aspects of blood-borne viruses and STD infection.
- ◆ To inform the development and implementation of policy and practice with respect to prevention and to the management of the HIV/AIDS epidemic.

Training and education

- ◆ To provide tangible opportunities and encouragement for postgraduate and post-doctoral training of scientific and medical staff in the epidemiology of HIV/AIDS, blood-borne viruses and sexually transmitted diseases.
- ◆ To disseminate the results of the Centre's research through all possible means, including presentations at national and international meetings, publications, through the media, and in an annual report and to support the dissemination of epidemiological and clinical knowledge related to HIV/AIDS, blood-borne viruses and sexually transmissible diseases to relevant communities.

Other

To perform other roles which may be determined from time to time by the Director, in consultation with ANCARD and approved by the Department of Health and Family Services.

7.6 APPENDIX C RECOMMENDATIONS OF THE PREVIOUS REVIEW COMMITTEE

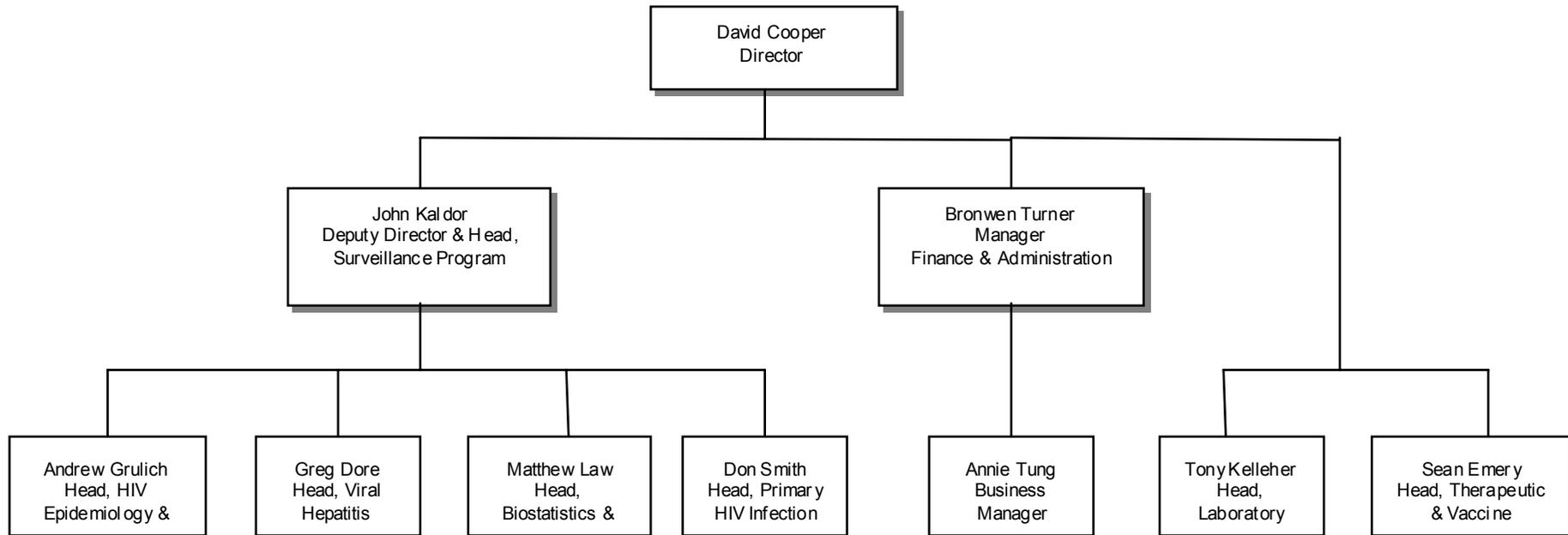
The previous review committee made the following recommendations:

1. The National Centre should receive core funding for the next five years to continue its work, with the next Review to be undertaken in 2002.
2. The Terms of Reference for the Centre should be amended in line with Section Seven of this report.
3. The Centre should continue and strengthen its work in relation to indigenous people as one of its highest priorities.
4. The Centre should continue to provide support to the National Indigenous Australians' Sexual Health Strategy 1996–97 to 1998–99.
5. The Sydney Men and Sexual Health (SMASH) cohort study should be stopped when the remaining proportion of the original cohort reaches 45 per cent. More representative behavioural information should be obtained by repeat cross-sectional studies.
6. Health services research undertaken by the Centre should encompass cost-effectiveness studies and studies regarding compliance with prophylactic and therapeutic regimens. The spectrum should encompass HIV/AIDS, hepatitis C virus (HCV) and, where appropriate, sexually transmitted diseases. The latter work should be consistent with the principles set out in the Third National Strategy.
7. The laboratory facilities and technical support staff to process, archive and, in the long term, maintain tissue samples, plasma, serum cells, DNA, RNA and viral isolates from individuals, cohorts or clinical trial participants should be separately funded and co-ordinated with the National Centre in HIV Virology Research. Funding, model rules of access and ethical principles related to the use of the materials should be clarified as a matter of some urgency.
8. An information strategy should be developed that supports the production of computer software incorporating an agreed set of data fields of relevance to studies of natural history, transmission, treatments and demographic features of HIV/AIDS. It is envisaged that baseline and annual data could be acquired, stored electronically at the site of care and, subject to the requirements of public health regulations and with appropriate consent of patients, used for research in approved projects.
9. An agreed set of demographic and clinical data should also be acquired for any laboratory research samples stored in the course of clinical or epidemiological studies. Data should include information regarding consent, sample collection conditions, timing, processing, de-identification coding, rules of access and guards to confidentiality.
10. Where opportunities exist, HIV natural history studies (in their broad sense including modification by treatment) should be conducted in ethnic-specific groups including indigenous Australians.
11. The Committee endorsed the view of the 1992 Review panel that the Community Health Research Network (CHRN) becomes an integral part of the Centre's program and management structure.
12. The Clinical Trials Working Groups should report directly to the Director of the Centre. The Director should be required to report to the Scientific Advisory Committee on any concerns raised by community representatives on the Working Groups.

13. The Centre, in addition to continuing its trials of new therapies, should increasingly address the important strategic questions in combination antiretroviral therapy.
14. Consideration should be given to convening a meeting of participants from all constituencies of the treatments community to discuss the advantages and disadvantages of observational databases in defining treatment strategies and regimens associated with improved outcomes.
15. There should be one Scientific Advisory Committee (SAC) for the National Centre, with responsibility for scientific standards and strategic planning of the Centre. Its composition should primarily reflect the scientific expertise needed to give appropriate guidance and advice to the Centre, as well as appropriate representation from the community, ANCARD and host institutions.
16. The SAC should take responsibility for advice and guidance of all aspects of the Centre's work, including clinical trials, with sub-committees established only where necessary to undertake detailed development of specific areas, for example in relation to non-HIV surveillance.
17. The Centre should produce a five-year rolling strategic plan, under the guidance of the SAC. This plan should be aligned with a budget that is presented in program format.
18. The Director should provide an annual report to ANCARD, endorsed by the SAC, and via RAC, on the progress of the Centre towards achieving its strategic goals.
19. Treatments advice should be the responsibility of a sub-committee of ANCARD, and responsibility for the clinical trials program and CHRN should be vested in the SAC.
20. The Clinical Trials and Treatments Advisory Committee (CTTAC) budget should be divided between clinical trials and treatments, with the clinical trials component being rolled into the Centre, and the treatments component allocated on the advice of the proposed Treatments Sub-Committee of ANCARD.
21. The current rules for application for Commonwealth competitively-awarded grants should continue to apply in relation to the core program of HIV research. Scope should be allowed for Centre staff to apply for grants to undertake research in related diseases or under special circumstances as approved by RAC. Initial expressions of interest should be examined by a joint committee of RAC and the NHMRC in order to make a ruling on eligibility.
22. The wording of the Third National Strategy should guide the activities of the Centre as far as the use of core funding to undertake work into related diseases is concerned i.e. those areas '... that have a clear and direct overlap with HIV/AIDS prevention strategies or target groups or are co-factors in HIV transmission'.
23. The Centre should be allowed to tender for work into related diseases such as hepatitis C and sexually transmitted diseases, particularly the co-ordination of national surveillance and natural history studies. These activities should be supported through commissioned or competitive project grants.
24. The Centre's role in the Asia-Pacific region should be encouraged and endorsed provided that the major efforts and resources put into such roles is limited to a small proportion of Centre core resources and that the majority of such activities are in the area of HIV.
25. The expertise of the Centre should formally be brought to the attention of AusAID and that AusAID be encouraged to utilise the expertise available in the Centre.

26. Discussion should be undertaken with AusAID during the current review of AusAID's Health Program to clearly delineate the relative expectations and responsibilities of AusAID and the Centre in relation to training and other assistance to countries in the Western Pacific and South East Asian Regions.

7.7 APPENDIX D MANAGEMENT ORGANISATIONAL CHART



Key



Executive Committee



Program Management Committee

7.8 APPENDIX E CURRENT STATUS OF SURVEILLANCE

	HIV	HCV	HBV	STIs
Passive reporting system	+++	++	+	+
Sentinel populations	+++ *	++ *	+	
Repeat surveys	++ **	++ **		

* STI clinics, blood donors, Defence Force.

** Injecting drug users.

Note: Work on standardising case definitions and risk factor recording is in progress for HCV. The work on hepatitis B virus (HBV) and STIs has just been initiated.