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COHORT PROFILE

Cohort Profile: Caribbean, Central and South America Network for HIV research (CCASAnet) collaboration within the International Epidemiologic Databases to Evaluate AIDS (IeDEA) programme

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How did the study come about?

The HIV/AIDS epidemic has evolved in its third decade to be an unprecedented human catastrophe of global scale and importance. Although an historic response for change and intervention has led to decreased rates of new infections and HIV-associated mortality in many communities, the enormity of the pandemic continues to overwhelm already constrained resources everywhere. Improved understanding of antiretroviral therapy (ART) responses and viral and host characteristics, both within and between diverse settings and populations, is needed to guide initiatives in HIV prevention and treatment worldwide.

The merging of existing clinical and research data related to HIV infection and its associated disorders answers questions that currently cannot be addressed using randomized trials or single sources of data. Cohorts such as MACS,¹ WIHS,²

HIVRN,³ EuroSida and the Swiss HIV Cohort⁴⁻⁶ have produced important observations regarding the epidemiology and long-term outcomes of HIV-infected individuals residing in North America and Europe, both before and after the era of highly active antiretroviral therapy (HAART). Assessments of short-term response to HAART in recently expanded single-site programmes have been reported globally.⁷⁻¹⁰ Collaborations such as TAHOD¹¹ and ART-LINC¹² have allowed short-term evaluation of antiretroviral programmes in resource-limited settings from several continents, and recently, comparisons of outcomes in the first year of ART between low- and high-income countries have been reported.^{13,14}

As access to ART becomes increasingly available, so does the amount of data related to patient treatment and care. Research should focus on developing collaborative databases that facilitate high-quality collection, harmonization and analysis of HIV-related data from clinical and research sites globally, with patient cohorts that include children as well as adults. Larger sample sizes will facilitate identification of rare outcomes and emerging problems, as well as permit the elucidation of more complex relationships involving use of HAART, comorbid conditions and other factors. Such efforts also would allow meaningful comparisons between treatment programmes that differ in their operational procedures and serve diverse communities in different countries. Unique features of individual sites exist, such as language used and cultural norms, research and care capacity, infrastructure development, personnel training and experience, and collection of data elements that differ in type, number, definition, or method of laboratory testing and established ranges of values. The use of innovative data and informatics approaches can

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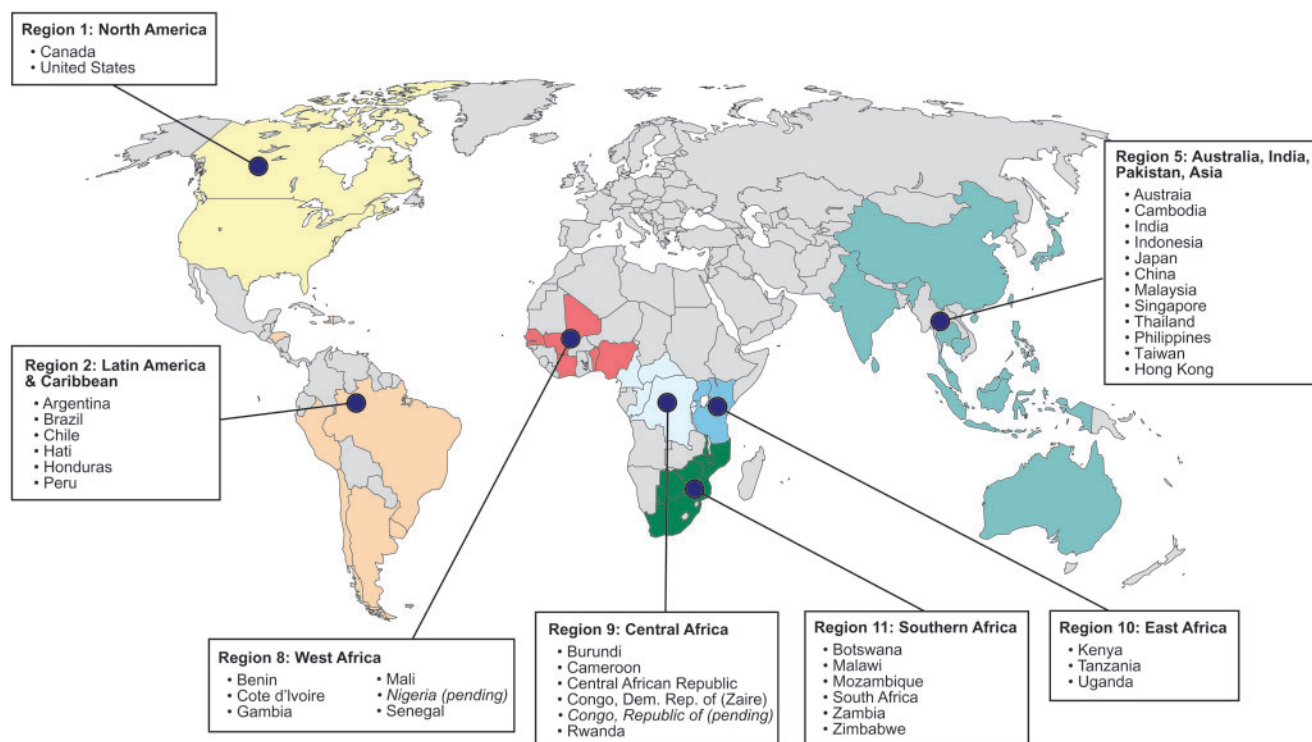


Figure 1 International Epidemiologic Databases to Evaluate AIDS (IeDEA) participating regions (from www.iedea-hiv.org).

provide a principled approach to meta-analysis of pooled data, and improve uniformity and consistency in data management in such heterogeneous settings.

A meeting held on September 28–29, 2004 in Bethesda, Maryland, brought together international experts in the field of HIV research to address both the potential and need for international collaborations. From that meeting, it was determined that there is interest, feasibility and necessity to combine data from different settings and cohorts to address those issues pertaining to HIV/AIDS which cannot be answered by single cohorts. As a result, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Request for Applications was released by the US National Institute of Allergy and Infectious Diseases (NIAID) and the US National Institutes of Health (NIH) on February 15, 2005. Applications were due by August 26, 2005. Four months later, all submitted grant proposals were peer-reviewed, and applicants representing seven of the twelve IeDEA regions received fundable scores (Figure 1). This article describes IeDEA Region 2: the Caribbean, Central and South America network for HIV research (CCASAnet).

The IeDEA initiative

The IeDEA initiative establishes international regional centres for the gathering and harmonization of high-quality and clinical HIV data and creates an international consortium to address key research questions in HIV/AIDS currently unanswerable by single cohorts. The sources of data include independently-funded investigators and clinical networks,

US and non-US cohorts, community-based facilities and academic medical centres and national and local databases. Data from more than 250 000 HIV-infected persons from 38 different countries are included in the IeDEA initiative (Table 1). Most regions anticipate expanding their collaborating cohorts during the 5-year funding period, and as regions gather data from HIV-infected children who have greater access to HAART, the number of children included will increase as well.

The IeDEA consortium proposes a scientific agenda that addresses relevant regional HIV research topics such as evaluating strategies that provide HAART to children and adults while optimizing HIV treatment adherence and the monitoring of care and clinical outcomes, particularly treatment toxicities in children and women. The natural history and complications of HIV infection and long-term ART will be described regionally, and the associations between aging, malignancy and HIV disease progression will be examined. The impact of HIV and tuberculosis, other opportunistic infections, hepatitis B or C coinfection and the immune reconstitution syndrome are areas of interest to the consortium, as well as genetic variation of HIV, including resistance patterns.

Although many of these research topics could be addressed using individual cohorts, the strength of the IeDEA initiative is the increased sample size attained by combining cohort data. This larger sample size permits for example, assessment of rare outcomes, comparison of different specific treatment regimens, or the ability to address questions that require specific subpopulations. By analysing data across IeDEA regions, the role of genetics (both host and viral) on the natural history of HIV infection and response to treatment may

Table 1 Regions funded and number of persons participating in IeDEA network

Region ^a	Countries	Regional operational and data management centre	No. of adults	No. of children	Total
1. Canada and United States (NA-ACCORD)	Canada, USA	Johns Hopkins University and University of Washington, USA	90 000 ^b	None	90 000
2. Caribbean and Central and South America (CCASAnet)	Argentina, Brazil, Chile, Haiti, Honduras, Peru	Vanderbilt University, USA	11 960	997	12 957
5. Asia and Australia (APHOD)	Australia, Cambodia, India, Indonesia, Japan, China, Malaysia, Singapore, Thailand, Phillipines, Taiwan, Hong Kong	University of New South Wales, Australia	4079	None	4079
8. West Africa (WADA)	Benin, Côte d'Ivoire, Gambia, Mali, Nigeria, Senegal	Institute of Public Health, Epidemiology & Development, France	33 245	2345	35 590
9. Central Africa	Burundi, Cameroon, Central African Republic, Democratic Republic of Congo, Republic of Congo, Rwanda	RTI International, USA	36 500	No. not specified	36 500
10. East Africa	Kenya, Tanzania, Uganda	Indiana University, USA	40 000	None	40 000
11. Southern Africa (OASIS)	Botswana, Malawi, Mozambique, South Africa, Zambia, Zimbabwe	University of Berne, Switzerland	32 012	3058	35 070
Total			247 796	6400	254 196

^aRegion number refers to the designation used by NIAID for each of the twelve competing regions that received funding through the IeDEA initiative.

^bNumbers are estimates provided by IeDEA (www.iedea-hiv.org), except for Region 1.²⁴

be evaluated. Individual cohorts of HIV-infected children have been small and by merging data from multiple cohorts the ability to make significant observations regarding HIV infection in the paediatric population is enhanced. Additionally, by standardizing the collection and definitions of data variables the quality and cost-effectiveness of observational cohort research will be improved.

The regional data centres form the IeDEA consortium and the principal investigators along with NIH programme officers constitute the IeDEA Executive Committee (EC). The EC identifies key information to be obtained across the participating sites, creates standardized definitions for clinical outcomes and events, and develops protocols for data collection, coding and merging. In addition, the EC identifies research questions to be addressed with multi-regional or consortium-wide data and reviews protocols from non-consortium investigators proposing collaborations with the IeDEA consortium. The Research Triangle Institute maintains the IeDEA website (www.iedea-hiv.org) and serves as the IeDEA Coordinating Center to coordinate consortium-wide activities.

CCASAnet core aims, organization and scientific agenda

CCASAnet brings together the biomedical informatics expertise of Vanderbilt University and the expertise in HIV medicine of clinical and research sites in Argentina, Brazil, Chile, Haiti, Honduras and Peru (Table 2). Core aims of CCASAnet are (i) to create and support a network of participating sites in the Caribbean and Central and South America for sharing of existing research and clinical data related to the epidemiology

of HIV and related disorders; (ii) to create a shared data repository and associated technologies for data merging that forms the union of data sets submitted by sites; (iii) to conduct and facilitate research using the shared data repository that enables answers to questions that cannot be answered by any single source; (iv) to develop and evaluate new biostatistical methods relevant to HIV epidemiology; (v) to develop a programme of education and training that will assist sites to improve the quality and consistency of their clinical research activities and (vi) to participate with other regional IeDEA networks in the development of international standards for sharing and meta-analysis of HIV-related data.

The CCASAnet Steering Group (SG) is composed of the Principal Investigators at each of the collaborating centres. It is responsible for providing input regarding the overall direction of CCASAnet projects and the use of CCASAnet data. The SG assumes responsibility for the conduct of research performed by the CCASAnet consortium, and identifies and addresses long-term technical and strategic issues regarding the collaboration. It reviews and approves proposals for internal and external CCASAnet projects and oversees the writing and publication of CCASAnet analyses. The Coordinating Center at Vanderbilt is the focal point for CCASAnet activities and management, including the collection, harmonization and merging of CCASAnet data. The CCASAnet Coordinating Center is accountable to the SG.

CCASAnet collaborations are research projects that use all or part of the CCASAnet data set, which is defined as any combination of the individual data sets submitted by CCASAnet sites or metadata maintained by the CCASAnet Coordinating Center. Participation in CCASAnet collaborations is on a project-by-project basis. Member sites are not required

Table 2 Program characteristics of sites participating in CCASAnet

	Argentina	Brazil	Chile	Haiti	Honduras	Peru
Site	Fundación Huésped Buenos Aires	Projeto Praça Onze Rio de Janeiro	Fundación Arriarán Santiago	Les Centres GHESKIO Port-au-Prince	Instituto Hondureño de Seguridad Social and Hospital Escuela Tegucigalpa	Universidad Peruana Cayetano Heredia Lima
Total no. of adult patients	2000	2800	1450	4000	1000	710
No. of adult patients on ART	1600	2500	1150	4000	750	500
Year of HAART expanded access	2000	1996	Late 2001	February 2003	July 2003	May 2004
Funding source for ART	MOH	MOH	PHS, GFATM	GFATM, PEPFAR, NIH	MOH	MOH, GFATM
Patients receiving free ART (%)	100	100	80	100	100	100
Generic ART use (%)	80	NRTIs, NVP, SQV, RTV are generic	0	80	90	90
HAART cost per month per patient (programme cost)						
First-line	\$104	Not applicable	\$190	\$82	\$52–100	\$30
Second-line	\$208	Not applicable	\$500	Not applicable	\$450	\$450
Guidelines used for ART initiation	National ^a	National ^b	National ^c	WHO ^d	National	National ^c
Measure of ART adherence	Patient self-report	Electronic registry of ART pick-up (monthly)	Electronic registry of ART pick-up (monthly)	Electronic registry of ART pick-up (monthly), pill counts, patient self-report	Registry of ART pick-up (twice monthly), patient self-report	Registry of ART pick-up (twice monthly)
Use of virologic monitoring	Yes	Yes	Yes	No	Yes (IHSS) Few (HE)	Yes
Viral genotyping/subtyping	Yes/Yes	Yes/Yes	Yes/No	No/No	Yes (few)/No	No/No
ID specialists at site providing HIV care (%)	100 (85% nationally)	100	100 (30% nationally)	Not applicable	40	100
Biological specimen archive	Yes	Yes	Yes (100)	No	No	Yes (300)
Active tracking of loss to follow up/percent loss to follow up	No/20	Yes/6	No/8	Yes/8	Yes/10 (IHSS) No/20 (HE)	Yes/25
Institutional Review Board	Local	Local and federal	Local	Local, national, Cornell, and Vanderbilt	Local	Local
Community Advisory Board	No	Yes	Yes	Yes	No	No

^awww.sadi.org.ar/images/RecomendacionesTAARV_SADI_2006.pdf^b<http://www.aids.gov.br>^chttp://www.minsal.cl/ici/guiasclinicas/vihsideR_Mayo10.pdf^dAs recommended by the Haitian government^ewww.minsa.gob.pe

ART, antiretroviral therapy; HAART, highly active ART; MOH, Ministry of Health; GFATM, The Global Fund to Fight AIDS, Tuberculosis and Malaria; PHS, Public Health Service; PEPFAR, US President's Emergency Plan for AIDS Relief; NIH, US National Institutes of Health; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; SQV, saquinavir; RTV, ritonavir; N/A, not available; WHO, World Health Organization; IHSS, Instituto Hondureño de Seguridad Social; HE, Hospital Escuela. Costs reported in US dollars. Approximate number of samples in given category is included in parentheses unless otherwise indicated.

to contribute data to or participate actively in every study or analysis project. By agreeing to collaborate on a scientific project, participants commit to supplying the requested and relevant data from their site, along with any metadata

necessary for interpreting the information. These data are then used only for the purposes defined in the specific project. The Coordinating Center maintains copies of data only as required by principles of scientific integrity, to support

Table 3 Patient cohorts of interest at participating CCASAnet sites

	Argentina	Brazil	Chile	Haiti	Honduras	Peru
ART-treated	Yes (1600)	Yes (2500)	Yes (1150)	Yes (4000)	Yes (750)	Yes (500)
ART-naive	Yes (400)	Yes (300)	Yes (300)	No	Yes (250)	Yes (210)
Tuberculosis cohort (HIV+)	Yes (450)	Yes	Yes (100)	Yes	Yes	Yes
Tuberculosis cohort (HIV-)	Yes	No	Yes	Yes	Yes	Yes
PMTCT, mother	Yes	No	Yes (50)	No	Yes	No
Infants born to seropositive mothers (HIV+)	Yes (130)	Yes (350)	Yes (15)	Yes (300)	Yes	Yes (52)
Infants born to seropositive mothers (HIV-)	Yes (150)	No	No	Yes	Yes	No
Women with subsequent pregnancies after receiving PMTCT therapy or ART	Yes (20)	Yes	Yes (20)	Yes	Yes	No
VCT, all serostatus	Yes (15 000)	Yes (4800 in year 2005)	No	Yes (24 114 in year 2005)	Yes	No
Discordant couples	Yes	No	Yes (50)	No	Yes	No
Well-documented acute seroconversion	Yes	Yes (40)	No	No	No	No

Approximate number of individuals in each cohort is included in parentheses. PMTCT, prevention of mother to child transmission; VCT, voluntary counselling and testing.

publications and any challenges to the validity of the data or its analysis that may arise.

Initial areas of scientific research focus on programmatic and patient characteristics that may influence the short-term outcome of ART in the region, including analyses of rates of and reasons for change in first-line ART. Other priorities for investigation include the evaluation of coinfections and malignancies important in the Latin America and Caribbean context (especially tuberculosis), as well as women's health issues, such as reproductive health and pregnancy and infant outcomes, and sexual-risk-behaviour prevention. Optimization of long-term ART outcomes will be studied in later years of the funding period, and biological specimen repositories will be expanded and used to examine viral and host genetic factors that may affect disease outcomes.

What does it cover and who is in the sample?

The combined sample size of the CCASAnet cohort is currently ~13 000 individuals, including 1000 children and adolescents. CCASAnet treatment programme characteristics are summarized in Table 2. HAART was introduced in Brazil in 1996, and between the years 2000 and 2004 for other sites. The rate of expansion of HAART delivery has been greatest in Haiti, where ~2500 patients began therapy over a 21-month period. The different CCASAnet sites receive funding from various sources, including local ministries of health, non-governmental organizations and NIH and other global health programmes. ART and care is provided free of charge to the majority of participants in the CCASAnet cohort. All programmes predominantly use generic drugs except in Chile, where the government has negotiated price reductions with the pharmaceutical industry, and in Brazil, where both locally produced generics

and brand name drugs purchased at reduced prices are used. Programme costs for first-line HAART regimens range from 30 to 190 US dollars monthly per patient, with higher costs incurred for second-line regimens at all sites. Eligibility for ART initiation is determined according to either national or World Health Organization guidelines,¹⁵ and all sites obtain CD4⁺ lymphocyte count at baseline.

The most common initial ART regimens utilized at all sites include the dual nucleoside reverse transcriptase inhibitor (NRTI) back-bone of lamivudine and either zidovudine or stavudine combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI). The exception is Brazil, where approximately equal numbers of patients start therapy with regimens based on NNRTIs and on protease inhibitors. In the other countries, protease inhibitor-based therapy is reserved mainly for treatment failures and most commonly includes lopinavir/ritonavir, indinavir, nelfinavir or saquinavir used in combination with NRTIs such as didanosine and abacavir. Second-line agents frequently used in Brazil also include atazanavir/ritonavir and tenofovir. Adherence to therapy is assessed by electronic registry of monthly ART pick-up at most sites. Measurement of plasma HIV-1 RNA levels at baseline or for suspected treatment failure is available at most sites, whereas HIV-1 genotype assays are used infrequently.

Each HIV treatment centre within CCASAnet implements a multi-professional team approach that includes physicians (mostly infectious diseases specialists), nurses, pharmacists, social workers, counsellors and community health workers. All participating cohorts are comprised of both ART-experienced and ART-naïve individuals (Table 3). Most CCASAnet sites also maintain data for special cohorts of interest such as HIV-negative and HIV-positive persons with tuberculosis, women that have received ART for the prevention of mother-to-child transmission of HIV, children of any serostatus born to HIV-positive mothers, and persons undergoing volunteer counselling and testing for HIV. In addition to data, biological

specimen archives are available for many individuals from most CCASAnet sites.

How often have patients been followed-up and what is measured?

Collaborating sites recruit patients and organize their follow-up locally, through routine clinical care and research protocols, and the frequency of follow-up varies according to the clinical status of the patient, time since ART initiation, and the presence of comorbidities and adverse effects of therapy. Data elements routinely collected from most CCASAnet sites include sociodemographic characteristics, specific ART including dates of treatment and reasons for discontinuation, use of other medications, presence of opportunistic infections and other non-AIDS diagnoses, laboratory parameters such as CD4⁺ lymphocyte counts, plasma HIV-1 RNA level, hemogram, liver function tests, serum creatinine, and serologies for hepatitis, syphilis, and toxoplasmosis (see Table 4 available in the online edition of the *International Journal of Epidemiology*). Overall programme characteristics of participating CCASAnet sites have been recorded (Table 2) and these assessments will be updated throughout the course of the project.

CCASAnet cohort data are based primarily upon medical records obtained as part of routine patient care. Most sites use paper charts to organize patient information, although some centres are transitioning to electronic medical records. Data management systems vary among CCASAnet sites, and methods used for collection, verification, and storage of data range from electronic clinical trials systems to locally developed spreadsheets and plain text files. In order to successfully merge the various pre-existing databases, the CCASAnet Coordinating Center is developing methods for capturing and storing the data and its descriptors in a flexible data exchange format.¹⁶

Several challenges are inherently imposed by the diverse nature of already collected data such as those included in the CCASAnet cohort. We envision many interesting and challenging analytical questions. Statistical methods to be developed for CCASAnet include sensitivity analysis approaches for causal inference,¹⁷ techniques for adjusting lab variables to enable fairer cross-site comparison,¹⁸ and unbiased and efficient sampling methods for studying the molecular epidemiology of HIV.¹⁹

What is the attrition rate likely to be?

Attrition is difficult to estimate at present. Loss to follow-up is defined differently for each CCASAnet cohort, and frequency ranges from 6% to 25% (Table 2). CCASAnet sites differ in terms of whether specific attempts are made to trace patients. Methods to ascertain death that may permit more accurate reporting of survival data, such as review of national and other death registries, obituaries and family interviews, are used to varying degrees at participating sites. The development of a uniform approach to determine vital

status will minimize bias in outcomes analysis for the CCASAnet consortium.²⁰

What protection of human subjects is used?

Institutional review board (IRB) approval for the CCASAnet collaboration has been obtained locally through each participating site as well as through the Vanderbilt Coordinating Center. Each collaborating site has its own local IRB, and Brazil and Haiti also seek approval through national ethics committees for certain studies. Each site maintains a Federalwide Assurance (FWA), indicating that their institution has agreed to conduct research according to the Common Rule.²¹ Les Centres GHESKIO in Haiti established its independent IRB in 1984 and has conducted research related to improving the informed consent process, especially in illiterate populations and in the social context of less-developed countries.^{22,23} The standardized evaluation of informed consent and other issues related to the ethics of transnational research are a planned focus of the CCASAnet collaboration. To maintain confidentiality, all data collected and merged by the CCASAnet Coordinating Center are de-identified by local centres prior to being transmitted to the Coordinating Center. Separate IRB approval will be sought for any projects that utilize biological specimens.

What are the main strengths and weaknesses of CCASAnet?

A principal strength of the CCASAnet consortium is that it includes several sizeable cohorts that reflect the regional HIV epidemic and represent a diverse spectrum of programmes, patients and care delivery. This variety permits analysis of the effects of regional and programmatic factors on individual patient outcomes in the Caribbean and Latin America. For example, the CCASAnet cohort will allow evaluation of antiretroviral efficacy and toxicity according to generic or brand manufacturer source. The inclusion of infants and children will improve knowledge of paediatric outcomes. Furthermore, the analysis of other special cohorts of interest, such as ART-naïve individuals, persons coinfecting with tuberculosis, and children born to HIV-infected mothers, may provide answers to questions of global importance. The capacity of CCASAnet to collaborate within the IeDEA network will contribute to the understanding of these and other global issues.

The CCASAnet cohort is composed of individuals from diverse genetic backgrounds, including African, Native American and European heritage, and the regional epidemic involves several recombinant viral subtypes. These features will allow analysis of the intersection of host and viral genetics with HIV disease outcomes within the region, and will contribute to genetic diversity studies as part of the global IeDEA network. Such projects will be possible in later years of the funding period through expansion of existing biological specimen repositories. Use of archived specimens also will permit determination and tracking of viral resistance patterns within the region.

The primary challenges of the CCASAnet collaboration arise from the same source as its strengths: the diverse nature of its region-wide data. Careful analysis of the data is required, since these values have been collected in different languages, with different measurement standards, and under varying conditions. CCASAnet investigators are developing and testing novel statistical approaches and improved data collection and harmonization methods in order to address many of these issues. Unlike a prospectively designed and implemented trial that adopts common data elements, data forms and quality control procedures, the specific data elements and the intervals between observations in the CCASAnet collaboration are a byproduct of heterogeneous local health care patterns.

How can I collaborate? Where can I find out more?

CCASAnet investigators agree to allow data from their sites to be merged and analysed for specific projects approved by the CCASAnet SG. Individual sites, however, retain primary ownership of their submitted data. The CCASAnet team welcomes research ideas from outside investigators and plans to actively pursue such external projects in the later years of the collaboration. Funded cohorts are currently limited to the six sites approved by NIH, though the team hopes to add new collaborating sites in future years. All such proposals for outside collaborations and for adding new collaborating cohorts will be reviewed by the CCASAnet SG. Readers who wish to find out more should visit the IeDEA and CCASAnet websites at www.iedea-hiv.org and <http://ccasanet.vanderbilt.edu>.

Supplementary material

Supplementary table can be found at *IJE* online (<http://ije.oxfordjournals.org>).

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References

- ¹ Mellors JW, Munoz A, Giorgi JV *et al.* Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;**126**:946–54.
- ² Bacon MC, von Wyl V, Alden C *et al.* The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. *Clin Diagn Lab Immunol* 2005;**12**:1013–39.
- ³ Gebo KA, Fleishman JA, Conviser R *et al.* Racial and gender disparities in receipt of highly active antiretroviral therapy persist in

- a multistate sample of HIV patients in 2001. *J Acquir Immune Defic Syndr* 2005;**38**:96–103.
- ⁴ Phillips AN, Grabar S, Tassie JM *et al.* Use of observational databases to evaluate the effectiveness of antiretroviral therapy for HIV infection: comparison of cohort studies with randomized trials. *AIDS* 1999;**13**:2075–82.
- ⁵ Egger M, May M, Chene G *et al.* Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;**360**:119–29.
- ⁶ May MT, Sterne JA, Costagliola D *et al.* The Antiretroviral Therapy (ART) Cohort Collaboration. HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. *Lancet* 2006;**368**:451–58.
- ⁷ Coetzee D, Hildebrand K, Boule A *et al.* Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;**18**:887–95.
- ⁸ Severe P, Leger P, Charles M *et al.* Antiretroviral therapy in a thousand patients with AIDS in Haiti. *New Engl J Med* 2005;**353**:2325–34.
- ⁹ Wolff MJ, Beltran CJ, Vasquez P *et al.* The Chilean AIDS Cohort: a model for evaluating the impact of an expanded access program to antiretroviral therapy in a middle-income country-organization and preliminary results. *J Acquir Immune Defic Syndr* 2005;**40**:551–57.
- ¹⁰ Tuboi SH, Harrison LH, Sprinz E, Albernaz RK, Schechter M. Predictors of virologic failure in HIV-1-infected patients starting highly active antiretroviral therapy in Porto Alegre, Brazil. *J Acquir Immune Defic Syndr* 2005;**40**:324–28.
- ¹¹ Zhou J, Kumarasamy N, Ditangco R *et al.* The TREAT Asia HIV Observational Database: baseline and retrospective data. *J Acquir Immune Defic Syndr* 2005;**38**:174–79.
- ¹² Dabis F, Balestre E, Braitstein P *et al.* The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Study Group. Cohort Profile: Antiretroviral Therapy in Lower Income Countries (ART-LINC): international collaboration of treatment cohorts. *Int J Epidemiol* 2005;**34**:979–86.
- ¹³ Braitstein P, Brinkhof MW, Dabis F *et al.* The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration and ART Cohort Collaboration (ART-CC) Groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006;**367**:817–24.
- ¹⁴ Tuboi SH, Brinkhof MG, Egger M *et al.* Discordant responses to potent antiretroviral treatment in previously naïve HIV-1 infected adults initiating treatment in resource-constrained countries. *J Acquir Immune Defic Syndr* 2007;**45**:52–9.
- ¹⁵ World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach, 2006. Available at: <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf> (Accessed February, 2007).
- ¹⁶ Duda SN, Cushman C, Masys DR. An XML model of an enhanced data dictionary to facilitate the exchange of clinical research data in international studies. *MEDINFO*, 2007 Brisbane Proceedings. *Int J Medical Informatics*. Suppl. In press.
- ¹⁷ Greenland S. Multiple-bias modelling for analysis of observational data. *J R Stat Soc Ser A* 2005;**168**:267–306.
- ¹⁸ Huang J, Brunelle R. A nonparametric method for combining multilaboratory data. *Drug Inf J* 2002;**36**:395–406.
- ¹⁹ Shepherd BE, Rossini AJ, Soto RJ, De Rivera IL, Mullins JI. Sampling designs for HIV molecular epidemiology with application to Honduras. *AIDS Res Hum Retroviruses* 2005;**21**:907–14.

- ²⁰ Anglaret X, Toure S, Gourvellec G *et al.* Impact of vital status investigation procedures on estimates of survival in cohorts of HIV-infected patients from Sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2004;**35**:320–23.
- ²¹ United States Department of Health and Human Services, Office for Human Research Protections. Federalwide Assurance (FWA) for the protection of human subjects. Available at: <http://www.hhs.gov/ohrp/humansubjects/assurance/filasurt.htm> (Accessed February, 2007).
- ²² Fitzgerald DW, Marotte C, Verdier RI, Johnson WD, Pape JW. Comprehension during informed consent in a less-developed country. *Lancet* 2002;**360**:1301–2.
- ²³ Fitzgerald DW, Pape JW, Wasserheit JN, Counts GW, Corey L. Provision of treatment in HIV-1 vaccine trials in developing countries. *Lancet* 2003;**362**:993–94.
- ²⁴ Gange SJ, Kitahata MM, Saag MS *et al.* Cohort Profile: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). *Int J Epidemiol* 2007, Advance Access published on January 8, doi:10.1093/ije/dyl286.

Appendix

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