knowledge = strength

Annual Review of the Canadian HIV Trials Network, **2001-02**

EVERYWHERE

NOW KNOWLEDGE

EQUALS STRENGTH IN

THE FIGHT AGAINST

HIV/AIDS

Message from the Directors

Everywhere now knowledge equals strength in the fight against HIV/AIDS. And, here in Canada, our Network continues to provide evidence of this close relationship in three main fields of activity: knowledge creation, knowledge transfer and capacity building.

Knowledge creation through clinical trials is the raison d'être of our Network. At the end of our twelfth year, March 31, we'd reviewed 173 trial protocols, approved 104 trials and implemented 77, with a total enrollment of 7,912 volunteers at 33 clinical sites across Canada. Another 11,000 Canadians had participated in our expanded access trials of promising new HIV therapies—life-savers, in many cases.

More significant, perhaps, our knowledge creators — physician-investigators, data experts, biostatisticians, clinical nurses, epidemiologists, and others — were working at full-capacity with 14 trials underway, four of which were brand new.

All these trials address urgent questions and Network priorities, such as therapy for people no longer benefiting from conventional combinations of anti-HIV drugs, co-infection, toxicity, adherence to drug regimens and vaccines and immunotherapies.

In last year's Message from the Directors, we highlighted two major phase III trials addressing the first priority: CTN 164 (Structured Treatment Interruption) and the tri-national CTN 167 (Options in Management of Antiretrovirals).

The CTN is also promoting highly innovative, smaller trials that reach further upstream in the research process. Take, for example, our 10-person phase I immune-reconstitution/therapy interruption study, CTN 140. Preliminary results after 104 weeks gathered by principal investigator Dr. Emil Toma of Montreal suggest that an unusual combination of treatment intensification (including the bone marrow stimulant GM-CSF) and the therapeutic vaccine Remune, followed by intermittent therapy and Remune boosters might allow people with chronic HIV to quit their HIV medications for extended periods without serious consequences.

Another smaller, innovative Network trial is a phase II study involving people co-infected with HIV and Hepatitis C. CTN 141 tests the effectiveness of a pegylated form of Intron, A, PEG-IFN, in combination with ribavirin, ddI and 3TC in antiretroviral-naïve co-infected patients attempting to eliminate the Hep C virus while controlling their HIV disease. This CIHR-funded study is led by Montreal's Dr. Marina Klein, one of a growing cadre of young CTN investigators who have previously been supported by CTN fellowships.

Reducing the toxicity of antiretroviral therapy is the focus of at least three trials approved or enrolling. These include CTN 148 (Gender Differences in Lipodystrophy Syndrome), CTN 157 (L-Carnitine plus Fenofibrate for Elevated Triglyceride Levels) and CTN 169 (d4T or Abacavir plus vitamin enhancement), which examines the management of elevated levels of lactic acid.

As Canada's HIV epidemic spreads among marginalized populations—injection drug users, Aboriginal people, women and others—we are also generating knowledge to help people without

access to effective HIV treatments. SPRINT (CTN 161) aims to do just this. This novel CIHR-funded trial, with sites in the United States and Argentina as well as Canada, tests the effectiveness and pharmacokinetic effects of a simplified protease inhibitor therapies.

SPRINT was designed by a CTN Pacific Region team led by Dr. Julio Montaner, a founder of our Network who was honoured in February by the German-based pharmaceutical manufacturer Boehringer Ingelheim with its $1 million Distinguished Researcher Award (see page 3).

Vaccines and immune reconstitution were the focus of a growing body of CTN research with seven different trials approved or underway. These include CTN 153, our phase-III prophylactic AIDSVAX B/B trial, led by researchers in Vancouver, Toronto and Montreal and CTN 173, a CIHR-sponsored pilot study involving Remune and ALVAC (canarypox vaccine), led by Drs. Jonathan Angel of Ottawa and Rafick-Pierre Sékaly of Montreal.

If the CTN is creating new scientific knowledge of the highest quality, it is also translating that knowledge swiftly to clinicians and the people they treat. For example, CTN investigators have been asked to rewrite HIV treatment guidelines in several provinces. And last year, our Network collaborated with community organizations to develop a popular clinical trials skills building workshop for treatment information workers and people with HIV.

Network capacity-building also had a banner year. Among other highlights, our Letters of Intent competition attracted a record 23 submissions. Researchers and community representatives from across the country ranked each of the submissions and a total of $150,000 was awarded for the development of seven new trial protocols.

As the CTN runs at full capacity and the HIV epidemic shape-shifts, we've had to focus our energies more keenly. Last year, therefore, our Network began developing plans for further boosting protocol development and trials activity in four critical core areas: antiretroviral therapies, vaccines and immunotherapies, co-infections and clinical management science. A national process will bring together teams of investigators with cross-cutting expertise in each area and forge new strategic partnerships with other networks—for example, the Canadian Network for Vaccines and Immunotherapeutics (CANVAC).

By focusing our intelligence in these core areas, our Network will continue to do what it does best: create and transfer useful knowledge and build capacity for future research of the highest scientific and ethical standards. In doing so we'll not only strengthen Canada's response to HIV/AIDS, we'll continue to set an example for HIV researchers and people living with this disease, everywhere.

DR. MARTIN SCHECHTER
NATIONAL DIRECTOR

DR. JULIO MONTANER
NATIONAL CO-DIRECTOR

DR. MICHAEL O'SHAUGHNESSY
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Events and Happenings 2001 - 02

Listing all trials A comprehensive electronic registry of all HIV clinical trials in Canada is under construction in a joint initiative launched in February by the CTN and the Canadian AIDS Treatment Information Exchange. As of mid August (2002), the registry included plain-language descriptions and other details of no fewer than 27 trials: 14 of which are being conducted outside the CTN. It is expected that the registry will be widely consulted by investigators, physicians, community organizations and people HIV. To check it out, click on Clinical Trials at www.hivnet.ubc.ca/ctn.html.

Network recruited one-third of participants in Canada-U.S. study Led by principal investigators Drs. Sharon Walmsley of Toronto and Sylvie Trottier of Quebec City, Canadian sites recruited no fewer than 253 volunteers—a third of the total enrollment—for one of the largest international comparative trials of protease inhibitors. CTN 102 / CPCRA 042, the NvR Study, which was co-managed by the United States Community Programs for Clinical Research on AIDS, looked at the relative efficacy of nelfinavir vs. ritonavir (or indinavir) in combination with nucleoside therapy for people with advanced HIV disease. Although the number of patients required to prove equivalence was not recruited, preliminary results show there was no difference in outcome of the two study arms. The study did demonstrate, however, that the use of combination therapy including a protease inhibitor has marked survival advantages over nucleosides alone, and many patients continued to do well without opportunistic infections or malignancies after 4-5 years on therapy. A detailed analysis of the resistance data to be released later this year will add to our knowledge of the relative benefits of the study drugs in first-line PI therapy.

Dr. Sharon Walmsley

Dr. Sylvie Trottier

Million-dollar professorship A new professorship in HIV/AIDS and population health at the University of British Columbia worth $1.6 million was established out of the generosity of CTN founder and National Co-Director, Dr. Julio Montaner. In February Dr. Montaner established an endowment for the research position with the $1 million he received as

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Dr. Julio Montaner

part of a Distinguished Researcher Award from Boehringer Ingelheim, the German-based pharmaceutical manufacturer. A partnership between UBC and the St. Paul's Hospital Foundation has so far added another $600,000 to the open endowment. The professorship is named in honour of the CTN's other distinguished National Co-Director (and Director of the B.C. Centre for Excellence in HIV/AIDS), Dr. Michael O'Shaughnessy.

CTN COMPETITION BREAKS RECORD Drug toxicity, adherence and immune reconstitution are the main concerns of seven proposed trials that won a total of $150,000 in protocol development awards in a letters-of-intent competition held by the Canadian HIV Trials Network. In all, the competition attracted 23 letters from researchers in four of the CTN's five regions, almost double the highest number of letters received in previous contests.

CANADIAN RESEARCHERS STATE PRIORITIES No fewer than 40 leading HIV researchers in basic and clinical sciences as well as social sciences and population health and community representatives from across Canada met with representatives of the Canadian Institutes of Health Research in Montreal, October 17, to discuss research priorities. The event was organized by the CTN and the Institute of Infection and Immunity. Among other recommendations given to the Institute's Scientific Director, Dr. Bhagirath Singh, participants called for a central office of HIV/AIDS research within CIHR, linked databases for clinical research and a "CTN-like network structure" to foster research in population health and social sciences.

RUEDY RETURNS Dr. John Ruedy, a co-founder of the CTN who left the Network eight years ago to become Dean of Medicine at Dalhousie University, then Vice-President, Academic Affairs, for Halifax's Capital District Health Authority, succeeded Dr. Stanley Read as chair of the Network's Scientific Review Committee in October. Among his first tasks, he worked with fellow committee members to develop new guidelines, including the adoption of the CIHR's four-point rating system.

Dr. John Ruedy

TRIALS STARTING 2001-02

CTN 158 CpG ODN 2006 as an Adjuvant and Immune Modulator

Summary: This study has two different arms: a susceptible arm and an immune arm, with respect to hepatitis B. In the susceptible arm, it will assess the safety and immune effect of CpG ODN 2006 as an adjuvant to a licensed hepatitis B (HB) vaccine in HIV-infected volunteers who have not been vaccinated or who have sub-protective levels of HB antibodies despite prior vaccination. In the immune arm, it will assess the safety and immune response to CpG ODN 2006 alone as a modulator of general and specific immunity. Participants must be on at least three antiretrovirals for the last six months, with an undetectable viral load for the last three months and a CD4 count above 200 cells/ml. Their combination therapy must comprise at least one protease inhibitor or efavirenz. A total of 40 HB-susceptible and 20 HB-immune volunteers will be enrolled. They will be randomly divided to receive either CpG ODN 2006 or a placebo, with hepatitis B vaccination if non-immune.

Principal Investigator: Dr. Bill Cameron, Ottawa Hospital.

Enrollment: 60.

Sites: Ottawa.

CTN 161 Simplified Protease Inhibitor Trial

Summary: This study will test the effectiveness and safety of simplified dosing schedules for two protease-inhibitor therapies for HIV infection. Participants will be randomly assigned to take either a saquinavir Soft Gel Capsule (SGC) 1600 mg and ritonavir 100 mg combination once a day, or an indinavir 800 mg and ritonavir 100 mg combination twice a day. In addition to testing the effect of the viral load and the safety and tolerability of the treatment regimens, 12 participants from each treatment group will be assessed frequently over a two-day period to measure the levels of the studied protease inhibitors in their blood. The study aims to recruit a total of 150 participants for a treatment period of 48 weeks from multiple study centres in Canada, Argentina and the United States.

Principal Investigator: Dr. Julio Montaner, St. Paul's Hospital, Vancouver.

Enrollment: 40 in Canada, 150 internationally.

Sites: Halifax, Toronto, Montreal, Vancouver and Victoria.

CTN 167 Options with Antiretrovirals (OPTIMA)

Summary: In this trial, volunteers with advanced HIV disease, and in whom regimens that have included all three classes of antiretroviral drugs have failed, will randomly be assigned to an intended antiretroviral drug-free period of at least three months or no drug-free period, and will be randomly assigned to receive either a standard antiretroviral therapy (ART) or a mega-ART (five or more drugs). This three-and-a-half-year study aims to enroll 1,700 participants in Canada, the USA and the United Kingdom. All patients will receive optimal prophylaxis against opportunistic infections. Since OPTIMA is a clinical management trial comparing treatment strategies, all available anti-retroviral medications can be used for treatment of study participants, including investigative new drugs in expanded access programs.

Principal Investigator: Dr. Bill Cameron, Ottawa Hospital.

Enrollment: 400 in Canada, 1700 internationally.

Sites: Halifax, Toronto, Hamilton, Kingston, London, Ottawa, Montreal, Quebec City, Sherbrooke, Saskatoon, Winnipeg, Edmonton, Calgary, Vancouver and Victoria.

CTN 169 D4T or Abacavir plus Vitamin Enhancement (DAVE)

Summary: The purpose of this study is to determine the best way to treat people on d4T with high levels of lactic acid. Participants will be randomly assigned to one of four groups. Group 1 participants will continue to take d4T as part of their antiretroviral regimen, and will be given the vitamin supplements. Group 2 will continue to take d4T without vitamin supplements. Group 3 will switch from d4T to abacavir and receive the vitamins. Group 4 will switch from d4T to abacavir without vitamin supplements. The study plans to recruit 80 participants from Canada and Argentina for a treatment period of 16 weeks and a follow-up visit at week 24.

Principal Investigator: Dr. Julio Montaner, St. Paul's Hospital, Vancouver.

Enrollment: 40 in Canada, 80 internationally.

Sites: Toronto, Calgary and Vancouver.

TRIAL

CTN 114 SCH 56592 vs. Fluconazole for Thrush

Results: Data analysis was performed on the 437 participants who received at least one dose of study medication and had a positive culture for thrush at visit 1. This revealed that oral therapy of thrush with posaconazole is as effective clinically as fluconazole in HIV-positive patients. In addition, both drugs were well tolerated with few adverse events. Posaconazole appears to be an effective alternative for thrush in HIV-positive patients.

Principal Investigator: Dr. Peter Phillips, St. Paul's Hospital, Vancouver.

Enrollment: 34 in Canada (485 Internationally).

Sites: Halifax, Montreal and Vancouver.

Objective: This trial examined the safety, tolerability and efficacy of four doses of posaconazole (SCH 56592), compared to fluconazole in the treatment of oropharyngeal candidiasis, or thrush, in HIV-positive patients. Ultimately, the study would evaluate if posaconazole can be a therapeutic option for thrush. This was a multicentre phase II, randomized, double-blind, parallel-group, active-control comparative study. HIV-positive participants with a fungal infection in the mouth and/or throat were randomized to receive either 50, 100, 200 or 400 mg of posaconazole, or fluconazole 100 mg daily for 14 days. The study was designed to compare the clinical success between the groups, defined as the absence of lesions and symptoms or minimal symptoms on day 14. The study also looked at the fungal response based on quantitative fungal culture measurements.

RESULTS 2001-02

CTN 117 Intermittent Rifabutin for MAC & TB

Results: Rifabutin exposures were similar at 4 and 8 weeks and had minimal effect on ritonavir and saquinavir exposures. Intermittent rifabutin dosing (150 mg every 3 days or 300 mg every 7 days) over 8 weeks provided a safe and manageable regimen for concurrent therapy with a combination of ritonavir and saquinavir.

Principal Investigator: Dr. Keith Gallicano, Ottawa Hospital.

Enrollment: 24.

Sites: Ottawa and Toronto.

Objective: CTN 117 aimed to determine if rifabutin, when given with both ritonavir and saquinavir, could be given once or twice a week instead of once daily. The study also observed the safety and tolerance of the three drugs during eight weeks of coadministration. This was a two-centre, randomized, three-period, two-group pharmacokinetic (drug-activity) study. In period 1, all participants continued their antiretroviral therapy alone and the blood concentrations of the two protease inhibitors were determined on day 1. In period 2 and 3, participants were assigned to receive either 300 mg every 7 days (group 1) or 150 mg every three days (group 2) of rifabutin in the morning for eight weeks with the protease inhibitors. In period 2, blood pharmacokinetics of rifabutin, ritonavir and saquinavir were assessed over their dosing intervals after 4 weeks of concomitant administration. In period 3, the same pharmacokinetic evaluations were performed after 8 weeks of concomitant administration.

CTN 118 Once daily adefovir + didanosine + lamivudine + nevirapine

Results: The study started in March 1999 and had recruited 27 participants at 7 sites across Canada when, in November of the same year, Health Canada requested that it be stopped owing to concerns over potential renal toxicity of adefovir dipivoxil. Early termination precluded recruitment of the planned number of participants (150). The data analysis was, however, performed and showed that renal toxicity was not observed in the investigational arm, which included adefovir, and that both regimens resulted in decreased viral loads and improved CD4 counts over 24 weeks. The study demonstrated the feasibility of a once-daily regimen.

Principal Investigator: Dr. Julio Montaner, St. Paul's Hospital, Vancouver

Enrollment: 27.

Sites: London, Hamilton, Toronto, Montreal, Sherbrooke, Calgary and Vancouver.

Objective: This study compared the antiviral effect and safety of a once-daily investigational four-drug regime (IDR) which included adefovir dipivoxil to a standard triple drug regimen (SDR) consisting of two nucleosides and a protease inhibitor. This was a 24-week open label study. Participants were randomized to receive the standard care or the investigational once daily regimen.

CTN 143 Twice daily indinavir + ritonavir (BEST)

Results: The data showed that both study arms were equivalent in reducing the viral load. A better safety profile was observed in the arm continuing indinavir three times a day. While this may be in part explained by the use of the liquid formulation of ritonavir at the beginning of the study, in a substantial proportion of patients this may be related to ritonavir boosting indinavir levels and hence increasing indinavir-related side effects.

Principal Investigator: Dr. Julio Montaner, St. Paul's Hospital, Vancouver.

Enrollment: 7 in Canada (326 internationally).

Sites: Vancouver.

Objective: CTN 143 compared continued indinavir 800 mg three times a day versus switching to indinavir 800 mg plus ritonavir 100 mg twice a day. This was a randomized, open-label, multicentre clinical trial, in stable HIV-infected patients on indinavir plus two NRTIs with viral loads below 500 copies/ml.

CTN 149 Saquinavir + ritonavir + 2NRTIs vs. efavirenz + 2NRTIs

Results: The 24-week analysis revealed that 60% of the participants in the saquinavir/ritonavir group reached a viral load below 50 copies/ml compared to 78% in the efavirenz group. When only the participants remaining on treatment were analyzed, the percentage of participants reaching a viral load below 50 copies/ml was 83% and 90%, respectively. The study concluded that the saquinavir/ritonavir was a convenient once daily protease inhibitor regimen that provided potent HIV suppression. The difference between the two arms in the intent-to-treat analysis was likely due to gastrointestinal tolerability problems with the soft gel formulation of saquinavir (Fortovose®).

Principal Investigator: Dr. Julio Montaner, St. Paul's Hospital, Vancouver.

Enrollment: 15 in Canada (159 internationally).

Sites: Toronto, Montreal and Vancouver.

Objective: This trial evaluated the antiviral activity and safety of saquinavir SGC/mini-dose ritonavir once a day in comparison with that of efavirenz in HIV-positive patients. This was a 48-week, multicentre, open-label study, where participants with a viral load of at least 5,000 copies/ml, a CD4 count above 75 cells/mm3, and no more than two weeks of antiretroviral therapy were randomized to receive either saquinavir SGC 1600 mg + ritonavir 100 mg once a day or efavirenz 600 mg once a day, each in combination with two nucleoside analogs.

CTN 151 Multiple Drug Rescue Therapy

Results: After the start of the study, new drugs became available. As a result, the drugs used in the two groups were essentially identical and the study was terminated. An analysis of the data from the 28 patients enrolled was, however, performed. In conclusion, additional information obtained from baseline phenotypic testing did not substantially affect the complexity, tolerability or efficacy of MDRT regimens. The widespread use of boosted PI regimens during this study probably affected this outcome.

Principal Investigator: Dr. Julio Montaner, St. Paul's Hospital, Vancouver.

Enrollment: 28.

Sites: Vancouver.

Objective: CTN 151 set out to determine if phenotypic resistance testing can help in the design of a multiple drug rescue therapy (MDRT). Participants in this 48-week study had experienced the failure of two or more antiretroviral drug regimens and had multiple virtual phenotypes revealing decreased susceptibility to at least two classes of antiretroviral medications. They were randomly assigned to receive either the "full" MDRT or the "sensitivity-based" MDRT. Full MDRT was a regimen of up to ten antiretroviral drugs, selected according to previous history of tolerability and laboratory test results. Sensitivity-based MDRT consisted of at least four drugs chosen from the full MDRT regimen, excluding those drugs to which the virus was highly resistant (or had lost sensitivity).

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