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Delivering on the pledge

treating the most vulnerable

Ensuring affordable AIDS drugs for children in the developing world

by streamlining Canada's Access to Medicines Regime

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Canadian HIV/AIDS Legal Network | Réseau juridique canadien VIH/sida

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Overview

Almost five years ago, Canada responded to the urgent need for medicines in many developing countries by creating "Canada's Access to Medicines Regime", with the goal of getting more affordable, generic medicines to patients in the developing world. Unfortunately, that laudable initiative was, and is, seriously flawed. But now there is a chance to fix it, helping thousands of people in developing countries survive — and in particular, helping prevent the deaths of thousands of children.

The United Nations estimated in 2007 that there were 33 million people living with HIV, including 2.5 million children. Roughly 95 percent of them live in developing nations. Over 8,000 people worldwide die of HIV/AIDS each day.

The law creating Canada's Access to Medicines Regime (CAMR) was passed by Parliament in May 2004 — with unanimous support from all political parties. Yet in all the years since, CAMR has been used only once. Why? Because the law has severe shortcomings. Both the companies that make generic medicines and the developing countries that need them are reluctant to face the bureaucratic burden of the current law. Unless it's fixed, CAMR may never be used again — and people who cannot get affordable medicines will pay the price.

The good news, though, is that CAMR can easily be simplified... without any additional spending.

In testimony and submissions to Parliament, the Canadian HIV/AIDS Legal Network and other organizations have outlined how CAMR can be streamlined by moving to the 'one-licence solution' described here. The timing is crucial. Lives are being lost each day. Amendments to the legislation are being prepared and, just as importantly, a private company is stepping up to the plate.

Canada's largest generic pharmaceutical manufacturer has made the commitment that, if CAMR is simplified, it will produce a lower-cost children's version of a key AIDS drug for export to developing countries under CAMR.

Those medicines are needed urgently. Parliament needs to act urgently to make CAMR work to help some of those who are most vulnerable. Canada can still deliver on the pledge made when it created CAMR.

Background

In May 2004, Parliament unanimously passed a law creating CAMR, an initiative that was supposed to address the urgent need for treatment for patients with HIV and other health problems. However, CAMR's processes and requirements are unnecessarily cumbersome and are ill-suited to the practical realities facing developing countries and generic manufacturers. Sadly, these have proven to be a disincentive to its use. In more than four years, only one country (Rwanda) and one Canadian generic manufacturer (Apotex Inc.) have used the regime, with a first shipment of an AIDS drug in October 2008.

While this is a tremendous breakthrough for several thousand people living with HIV in Rwanda who will get life-saving treatment, this one shipment took years of effort; these medicines are getting to patients *despite* all the hurdles in CAMR, not because CAMR is truly workable. Indeed, all evidence suggests CAMR is unlikely to be used again unless it is simplified. CAMR does not work for either the potential purchasers and beneficiaries of more affordable medicines, nor the potential suppliers of those medicines. It needs to be fixed.

Canadian non-governmental organizations (NGOs), legal experts and other advocates have made concrete recommendations for reforming CAMR to remove the red tape. Those recommendations are informed by the experience with the one use of CAMR to date, as well as by input from international legal experts and those directly involved in procuring medicines in and for developing countries. In broad terms, the recommended reforms are essentially the same as those that have been put forward by generic pharmaceutical manufacturers in Canada, including Apotex, the one company that has been through the CAMR process. There is a basic consensus across all these experts that CAMR needs to be fixed. Yet the Government of Canada has, to date, taken the position that it is premature to reform CAMR, even as the global AIDS pandemic and other diseases cause preventable suffering and death.

This backgrounder outlines the urgent need for practicable, affordable paediatric formulations of AIDS medicines and the prospects for reforming CAMR to address that need.

Dying for drugs: forgotten children in the developing world

In sub-Saharan Africa, HIV has become one of the major killers of young children. According to the Joint UN Programme on HIV/AIDS (UNAIDS), more than 2.3 million children under the age of 15 are infected with HIV, and approximately 90 percent of them are in sub-Saharan Africa.[1] Of the estimated 780,000 in need of antiretroviral (ARV) treatment, only 15 percent are on treatment, and in Sub-Saharan Africa this number falls to 6 percent.[2] Reflected in these statistics is the reality is that in the developing world, half of children infected with HIV will not live to see their second birthday.[3] Yet early treatment within the first few months of life can dramatically improve the survival rates of children with HIV. A recent study in South Africa found that mortality was reduced by 75 per cent in HIV-infected infants who were treated before they reached 12 weeks of age.[4]

"Children infected in early infancy usually die before the age of two. There are more than half a million deaths of children from AIDS every year. ... It leaves the mind reeling to think of the millions of children who should be alive and aren't alive, simply because the world imposes such an obscene division between rich and poor."

— Stephen Lewis, UN Secretary-General's Special Envoy for HIV/AIDS in Africa, World AIDS Day, December 1, 2005

Treating HIV positive children in the developing countries: the challenges

In a major report released a few years ago, the World Health Organization (WHO) recognizes that there is a critical need to provide ARV therapy for infants and children with HIV.[5] The report highlights that in countries where this has been done, infants and children with HIV now survive to adolescence and adulthood.

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However, scaling up treatment for children with HIV faces several obstacles, such as: the lack of affordable simple diagnostic tools; infrastructure and delivery problems; insufficient understanding that ARVs work in children; and above all, a lack of affordable, practicable antiretroviral formulations for children. The WHO report identified that:

> ...adherence in children is a special challenge because of factors relating to children, caregivers, medications and the interrelationship of these factors. The lack of paediatric formulations, poor palatability, high pill burden or liquid volume, frequent dosing requirement, dietary restrictions and side-effects may hamper the regular intake of required medications.[6]

The WHO report recognizes that medicines in the form of syrups and solutions remain necessary for treating very young children and infants that have problems swallowing. But it also urges that large volumes of liquid or syrup formulations should be avoided where possible, for various reasons. Syrups are often only available in limited quantities and at high cost. They are more difficult to store, including requiring refrigeration in some cases. They often have a reduced shelf-life, taste unpleasant and are harder for parents or caregivers to administer, all of which make it harder to ensure children get the right amounts of medicines at the right times. They are very cumbersome to transport, which makes them ill-suited for more remote settings and settings where transportation infrastructure is weak. All of these factors mean other options are critical for treating patients, and in particular infants and children.

"We have some syrups, but I don't particularly like using them as they are complicated to teach someone to use and fraught with error."

— Dr. Adrienne Chan, Dignitas Medical Coordinator, Zomba (Malawi)

In East Africa, for example, a recent report by the UN Development Program (UNDP) found access to essential medicines for HIV treatment is beyond the reach of a large percentage of

the infected population in the EAC.[7] With more than 6 million people living with HIV and an average HIV prevalence rate exceeding 5 percent, providing a good standard of care and treatment places an enormous burden on available services and support systems. This burden is primarily due to the high price of essential medicines. Although access to ARVs has expanded considerably in recent years, the sheer scale of need in the region means that only a small percentage of the persons in need of ARVs are receiving treatment.

The problems of access to affordable AIDS medicines are further compounded for children living with HIV/AIDS because of the lack of "fixed-dose combinations" (FDCs) — that is, formulations that combine several AIDS medicines in one tablet — to replace individual solutions. In just four East African countries, there are over 135,000 children currently in need of AIDS treatment.[8] During a UNDP field mission to the region in August 2007, people working on the front lines repeatedly reiterated the need for simplified children's formulations of ARVs. Doctors, nurses and procurement officers repeatedly refer to the problems of adherence, supply storage and the burdensome nature of transporting large quantities of the paediatric ARV syrups from the local hospital dispensary to patients' homes.

To address these issues, the WHO identifies two key recommendations for those designing policies and programs to improve AIDS treatment, and for health-care workers treating patients:

1. There is a need to standardize and simplify ARV regimens for children.

2. When choosing regimens, decision-makers should consider ways to minimize the challenges faced by the child and caregivers regarding medications and best fit the ARV regimens into the life circumstances of the child and caregivers.

In the 7 months that he worked at the Tsepong Clinic in Lesotho, Dr. Philip Berger witnessed first-hand the difficulty that caregivers, who were primarily grandparents, experienced trying to administer the correct dosage of the antiretroviral syrups to their grandchildren infected with HIV:

"The grandparents were often confused about the required dosage and found it difficult to measure out the exact amount the child needed. Paediatric solid formulations would greatly ease the administration of treatment for HIV-infected sick children and dramatically increase the probability of treatment success. Paediatric formulations which contain all necessary antiretrovirals in one dose are absolutely necessary."

— Dr. Philip Berger, Tsepong Clinic (Lesotho) and St. Michael's Hospital (Canada)[9]

FDCs for children: a patient-friendly solution

To respond to the need for practical solutions, the WHO encourages the use of fixed-dose combinations (FDCs) "when formulations of assured quality and proven bioequivalence are available as they offer operational advantages." By combining multiple medicines, FDCs can improve adherence to ARV regimens, including for children, by simplifying treatment to just one or two pills a day; this in turn limits the emergence of virus that is resistant to the drugs. In the right form, FDCs also make it simpler to store medications and distribute them, particularly in settings where infrastructure for proper storage (e.g. refrigeration) and distribution (e.g., transportation difficulties) is limited or weak. However, there is a lack of FDCs of standard ARV medicines suitable for children. To scale up AIDS treatment, the WHO "…strongly encourages the development of formulations appropriate for paediatric use, particularly solid formulations (e.g. crushable, dispersible, granular, scored tablets or capsules that can be opened) in doses that can be used by paediatric patients under 14kg."[10]

Fixed-dose combinations that are both affordable and practicable are urgently required to help treat children with HIV. The WHO report recognizes that generic pharmaceutical companies must be encouraged to produce these drugs at an affordable price.

The WHO Paediatric Antiretroviral Working Group has concluded that "priority antiretroviral products required for treatment include the need for a 60/30/50mg tablet of zidovudine/lamivudine/nevirapine."[11]

"It is crucial to have zidovudine-containing FDCs in paediatric formulations to widen choice for children. The R&D pharmaceutical industry has not been interested in producing such a product ... due to different companies holding the patents for the constituent drugs of the FDC. It is also very important that there be more than one producer of a zidovudine-based paediatric FDC that is WHO-prequalified."

— Dr. David Hoos, MTCT-Plus Initiative, Columbia University (USA)[12]

Admittedly, the market for paediatric ARVs is smaller than the market for adult versions. However, there is a range of financing options, including the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), to assist developing countries in buying medicines. On the supply side, we need to make it straightforward for companies who believe they have a corporate responsibility to respond to this humanitarian crisis. If CAMR were more user-friendly, it could play a role in getting lower-cost, generic AIDS drugs — including FDCs suitable for children with HIV — to developing countries.

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One drug, one country in four years: CAMR is not an "expeditious solution"

In 2003, Canada and other members of the World Trade Organization (WTO) agreed that there needed to be an "expeditious solution" to the problems facing developing countries in gaining access to lower-cost, generic versions of medicines for public health problems such as HIV/AIDS. That agreement became the basis for Canada's law creating CAMR, one of the first such initiatives in the world. But years later, it's clear that neither CAMR, nor the similar laws adopted by a few countries, are the "expeditious solution" that was promised.

In 2008, Rwanda set a global precedent when, after an international competitive tendering process, it decided to buy a lower-cost, generic FDC from the Canadian manufacturer Apotex.. The compulsory licence issued under CAMR — the only such licence to date — authorizes the delivery of enough of Apotex's Apo-TriAvir to treat approximately 21,000 people living with HIV for 1 year. The selling price is about one-third of what it would cost if the brand-name drugs were bought separately.[13]

This breakthrough is welcome. It is the first such action in the world. However, more than 4 years have passed since CAMR was created by Parliament. A single use of the regime, to export one drug to one country in a limited quantity, is hardly a success; it is a drop in the bucket. If CAMR is to work as part of Canada's response to the global AIDS crisis and other public health burdens on developing countries, it must be streamlined. Access to workable AIDS medicines for children living with HIV is a particularly urgent need that should spur Parliament to make the necessary changes to CAMR.

> *"Fixed-dose combination products are needed in formulations that are palatable, that are easily transported and stored, and that can be administered to young children. Technology exists that is able to produce paediatric formulations of medications, but these products need to be able to reach children quickly to avoid deterioration in their health. In order to encourage generic companies to use their expertise to develop paediatric formulations and to ensure these drugs reach children expeditiously, CAMR needs to be amended to remove clauses that unduly delay the export of generic medications."*
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> — Dr. Joel Lexchin, School of Health Policy and Management, York University (Canada)[14]

Children in the developing world can't wait: CAMR needs reform now

In a review released in December 2007, the Minister of Industry concluded that "not enough time has passed and not enough evidence has accumulated to warrant making changes to CAMR." [15]

But patients can't afford further delay by the Government of Canada. Every day thousands of people infected with HIV die from lack of access to affordable medicines — one in two children with HIV in the developing world die before reaching their second birthday because they don't have access to the medicines needed to save their lives.

With all-party agreement in Parliament to the bill that created CAMR in 2004, Canada promised to be become a leader in helping developing countries gain sustainable access to affordable generic medicines by allowing "compulsory licensing" of patented medicines in Canada solely for the purposes of exporting them to those countries. But the CAMR legislation is seriously flawed: it is layered with restrictions and regulatory requirements that have hindered efforts to use it. Some of these are not even required under WTO rules — and to the extent that the cumbersome process for licensing does reflect an agreement reached at the WTO years ago, it's important to remember that countries also explicitly agreed that this one approach was "without prejudice" to other approaches. Since Canada was one of the first to adopt this sort of law, based on an agreement negotiated under the patent rules of the World Trade Organization (WTO), Canada is also well positioned to show global leadership in acknowledging that the current law does not offer the rapid, flexible, sustainable solution that is needed and was promised.

The one use of CAMR to date came about because of the years-long commitment of one Canadian generic pharmaceutical company and the ongoing pressure of NGOs and other outspoken advocates, and with considerable support and encouragement at the local level in Rwanda to take the necessary steps. At the time that commitment was made by the generic manufacturer, it was by no means certain that developing countries would, from their end, be willing or able to make use of the convoluted regime. Yet Apotex developed a fixed-dose combination that, at that time, did not yet exist at all because of patent barriers, and eventually concluded a deal with Rwanda to supply the product at a globally competitive price.

But this kind of effort cannot be sustained over and over — and it shouldn't be necessary. Unless CAMR is made more user-friendly for developing countries and generic manufacturers — the purchas-

ers and suppliers who need to use CAMR to benefit patients — it is unlikely to be used again. Waiting years longer to diagnose the problems with CAMR is unnecessary and results in real deaths that could be avoided. Rather, the limitations of the current regime have been identified repeatedly, including from the experience to date of efforts to use CAMR.

Fixing CAMR: what should be done?

Concrete solutions have been put forward to streamline CAMR so that it will be easier for both developing countries and generic medicine manufacturers to use to get more affordable medicines to patients in developing countries. In particular, the Canadian HIV/AIDS Legal Network has proposed 13 specific reforms that should be made to CAMR. Those proposals are endorsed by the wide range of Canadian NGOs belonging to the Global Treatment Access Group and by Stephen Lewis, former UN Special Envoy on HIV/AIDS in Africa. The central recommendation among those is to simplify the compulsory licensing process itself.

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Streamlining CAMR: a "one-licence solution"

Instead of the current country-by-country, order-by-order process of compulsory licensing currently found in CAMR, a better law would require just one licence on a patented medicine. That one licence would allow exports to any of the developing countries covered by the law without restricting the quantity in advance.

As a condition of the licence, the generic drug manufacturer would still pay royalties to the company with the patent on the drug based on the sales of the generic product. (The existing formula in CAMR for calculating royalties that must be paid on any given contract is perfectly adequate and provides clarity and certainty to all involved, including the generic manufacturer getting a licence.)

One process, one licence — easier and more adaptable for developing countries and for suppliers of generic medicine, and therefore better for patients who need life-saving medicines.

A one-licence solution would allow Canadian generic manufacturers to participate more easily in such programs and hence support their contribution to the effort to scale up treatment for children living with HIV/AIDS.

In its review of CAMR, the government said it would not rule out future amendments should circumstances change.[16] Circumstances have changed — for the worse. How many more caregivers have to go through the pain of holding and watching their children and grandchildren die before our government deems it is the right time to amend CAMR? As Canadians, we can no longer allow our government representatives to sit by while "monitoring" the situation and waiting for "enough evidence." It is time for us to insist our representatives uphold their commitment to improve access to medicines for the people in the developing world.

For more information

Canadian HIV/AIDS Legal Network, "Getting the Regime Right — Brief to the House of Commons Standing Committee on Industry, Science and Technology regarding Canada's Access to Medicines Regime", online via www.aidslaw.ca/camr.

1 WHO and UNICEF, "Scale up of HIV-related prevention, diagnosis, care and treatment for infants and children: A programming framework" (2008), page 11.

2 Ibid.

3 M-L Newell, H Coovadia et al, "Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis", Lancet 2004; 364: 1236.

4 UNICEF, UNAIDS and WHO, Children and AIDS (2008).

5 WHO, Antiretroviral Therapy For HIV Infection in Infants and Children: Towards Universal Access, Recommendations for a Public Health Approach (2006).

6 Ibid.

7 UNDP, Intellectual Property Law, Pooled Procurement and Access to Antiretroviral Therapy in the East African Community (2007).

8 WHO, Scaling up priority HIV/AIDS interventions in the health sector: Progress Report, April 2007.

9 Dr. Philip Berger is Chief of Family and Community Medicine at St. Michael's Hospital in Toronto, and one of Canada's foremost HIV/AIDS doctors.

10 WHO, Antiretroviral Therapy For HIV Infection in Infants and Children (2006), p. 19.

11 WHO Paediatric Antiretroviral Working Group, "Preferred antiretroviral medicines for treating and preventing HIV infection in younger children" (2007).

12 Dr. David Hoos is Assistant Professor of Clinical Epidemiology at the Mailman School of Public Health, Columbia University. He is a well-known recognized technical expert on HIV/AIDS policy and procurement and is currently a member of the Technical Review Panel at the Global Fund.

13 Apo-TriAvir combines three key AIDS drugs in one tablet: 300mg zidovudine, 150mg lamivudine and 200mg nevirapine. Apotex's price to Rwanda is 39 U.S. cents per daily dose (2 tablets a day at 19.5 cents per tablet).

14 Dr. Joel Lexchin is a physician and professor in the School of Health Policy and Management at York University.

15 Minister of Industry (Government of Canada), Report on the Statutory Review of Sections 21.01 to 21.19 of the Patent Act (December 14, 2007), online via www.camr.gc.ca.

16 Ibid.