ANTIRETROVIRAL THERAPY FOR CHILDREN IN THE PUBLIC HEALTH CARE SECTOR

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Because of the South African governmental health policy, which does not permit public health service access to antiretroviral drugs (ARVs), the use of these drugs has been restricted to clinical trials and to the upper tier of health care services in South Africa, i.e. patients who have health care insurance or other means to purchase drugs. Clinical experience with ARVs has been restricted to physicians in private practice and those engaged in drug trials. Since South African children have rarely been enrolled as subjects in drug trials, few local paediatricians in hospital or academic practice have been able to gain experience in using highly active antiretroviral therapy (HAART). Moreover, few public health care institutions, whether urban or rural, have yet developed the sort of dedicated, comprehensive clinical HIV service that is an essential precondition for the successful introduction of HAART.

FUNDS FOR ARVs TO TREAT CHILDREN IN THE PUBLIC SECTOR

Vertical transmission of the HIV from mother to child accounts for the vast majority of HIV infections seen in South African children. Prevention of mother-to-child transmission (pMTCT) is highly cost-effective in comparison to hospital care of HIV-infected children,[1,2] but the cost and cost-efficacy of HAART in the local setting has not yet been included in this calculation. If pMTCT programmes are rolled out efficiently and if HAART becomes available for use during pregnancy, we may expect mother-to-child transmission rates of less than 1%. Far fewer children would need HAART and the overall cost may be more acceptable to many.

In the absence of efficient pMTCT, paediatric services countrywide have seen steep increases in admissions and outpatient visits for HIV-related infections during the past decade, even in provinces with lower rates of adult infection.[3] Where children have reasonable access to health care, a considerable number follow a chronic disease course,[4] require recurrent hospital admissions and present an increasing burden of cost[5] to the public health service.

At present the right of HIV-infected children to 'standard of care' management, including HAART, is void unless health care workers in the public service look beyond government for funds to support HAART for their patients. We need to engage with foreign charities, the Global Fund against tuberculosis, malaria and AIDS, and organisations like the Treatment Action Campaign to find ways to help our patients. Because HIV infection and AIDS are new to our region we need new and additional sources of money and not merely a redistribution of what was an inadequate health care budget to start with.

Partnerships between foreign donors, local non-governmental organisations (NGOs) and public service hospitals offer a model (Fig. 1) through which indigent patients can gain access to HAART. The foreign donor is the source of funding. NGOs administer these funds and account for expenditure to the donor. Public service hospitals and clinics provide the staff and infrastructure.

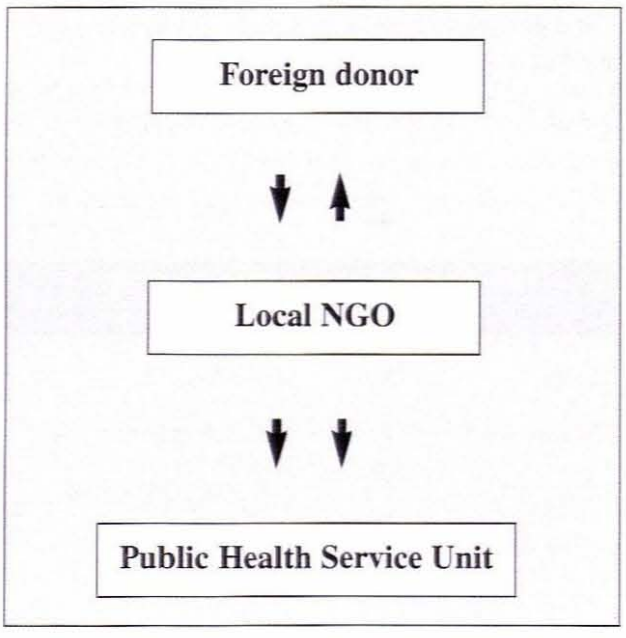

Fig. 1. A partnership to deliver HAART in the public sector.

Various forms of such partnerships already exist and have enabled doctors at several public service hospitals to initiate pilot HAART programmes. The benefit of these partnerships is that they hasten access to treatment and offer sites at which staff can be trained in the use of ARVs. A potential harm of this model is that the pressure on government to provide meaningful funding for HAART may be lifted. Pilot treatment programmes may permit decision-

makers to delay the roll-out of definitive services.

Besides their obvious benefits to infected children, HAART pilot projects are useful for other reasons. While it is true that many patients with HIV infection,[6] and indeed simple, first-line HAART regimens, could be managed at primary care level, many paediatricians and paediatricians in training feel themselves inadequate to manage infected children.[7] Pilot programmes offer an opportunity for health care workers to set up the necessary structures to provide comprehensive care, to acquire the necessary expertise and familiarity with treatment regimens, and to gain operational insights into practical requirements for successful management with ARVs. Pilot programmes will provide essential information on what facilities and staff are required to prescribe, dispense and promote adherence to HAART regimens in the public service.

WHICH CHILDREN SHOULD BE TREATED

The updated Southern African HIV Clinicians Society guidelines for the management of HIV infection in children list clinical category B or C disease and/or a CD4+ percentage below 20% of the age norm as indications for starting HAART. These guidelines are valid for children attending public service clinics and hospitals.

The cost of laboratory tests to confirm the diagnosis and time the initiation of therapy is a problem for implementing HAART in the public service. A polymerase chain reaction (PCR)-based test to make a definitive diagnosis of HIV infection before starting treatment in children under 18 months old is indispensable. A correct assessment of immunosuppression is difficult without access to CD4+ counts. A recent study has shown 85% of 'stable' infected children to be moderately or severely immunosuppressed.[8] There is some evidence for a positive correlation between CD4+ and total lymphocyte count. It would therefore seem reasonable to consider HAART in any child with category B or C disease and/or a low total lymphocyte count as a candidate for HAART.

As is the case with adults, starting treatment is seldom an emergency in children. However, since growth and development are impaired in the majority of HIV-infected children, and since both of these problems respond to HAART,[9,10] there seems to be more urgency to start treatment in the paediatric setting.

Patients with HIV infection attending public service institutions are at high risk of infection with *Mycobacterium tuberculosis*. Children who are receiving treatment for tuberculosis when first considered for HAART should complete TB therapy before starting treatment with ARVs if their immunity is moderately suppressed. Those with severe immunosuppression should preferably complete 2 months of intensive TB therapy before starting their HAART regimen. This reduces the chances of shared toxicity and a paradoxical worsening of TB with immune reconstitution. Children who are profoundly immunosuppressed should first start and be seen to tolerate antituberculosis therapy before starting antiretroviral therapy.[11]

RATIONING OF ACCESS TO A LIMITED TREATMENT RESOURCE

A limited number of children can be treated in charity-funded pilot programmes. The approach shared by several such programmes is to allocate HAART according to a queuing system: One treats those children who meet a set of inclusion criteria (based on the HIV Clinicians Society guidelines) and closes admission to the programme once the full budget and all available treatment slots have been allocated.

Some pilot clinics have elected to treat mothers and children in pairs. The reasoning behind such a decision is clear, but because the course of HIV infection in mother and child is so often asynchronous and because the disease generally runs a faster course in children, this approach may mean that many well mothers will have to watch their children die.

CHOICE OF A TREATMENT REGIMEN

The Southern African HIV Clinicians Society guidelines for ARVs in children provide a complete list of drugs available for children and recommendations regarding the combinations to be used. A first-line three-drug regimen should include a 'backbone' of two nucleoside reverse transcriptase inhibitors (NRTIs) together with either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Because children often have very high viral loads at diagnosis that are frequently not suppressed to undetectable levels, there is a high risk that resistant strains of virus will arise. Since NNRTI resistance requires a single mutation, the choice of a PI to complete a three-drug regimen may be preferable.

Most drugs are more expensive as paediatric suspensions than in tablet, powder or capsule form. Some paediatricians, driven by cost constraints, treat children with tablets that their caregivers are required to crush and suspend in carefully measured volumes of water before administration. The unfortunate paradox is that the home environments of the poorest patients tend not to have the space or facilities for such relatively complex preparations. Hence children attending public service clinics probably need the more expensive ready-made suspensions and the (also more expensive) simplest daily regimens – if their caregivers are to adhere to treatment. The majority of charity-funded HAART programmes have opted for relatively expensive, but simple, suspension-based regimens.

ADHERENCE TO HAART REGIMENS IN CHILDREN

HAART can achieve control of viral replication in HIV-1-infected children who adhere to therapy.[12] Medicine that is difficult to prepare or unpalatable is less likely to be administered to the child.[13] If caregivers are not prepared for adherence before starting HAART, or if regimens are too onerous to follow (Table I), treatment is likely to fail.

TABLE I. REASONS FOR NON-ADHERENCE TO PAEDIATRIC HAART REGIMENS[14]

- Unpalatable medicines
- Difficult formulations
- Problems around meals
- Non-disclosure to others
- Hiding or re-labelling medicines
- Defaults at clinic
- Midday doses

Every effort should be made to see the burden of adherence from the caregiver's point of view. Meticulous attention to detail offers the greatest likelihood of making HAART a successful joint venture (Table II). The key to adherence lies in the amount of time and care the health care worker can devote to the effort of explaining the purpose and practice of adherence.

TABLE II. STRATEGIES FOR THE PROMOTION OF ADHERENCE TO PAEDIATRIC HAART REGIMENS

- Promote **demand** rather than adherence
- Encourage maternal self-esteem
- Cohort bookings to promote alliance between mothers
- Buddy system for 'reciprocal DOTS' reward for good performance
- Promote pride in access, therapeutic programmes, national success
- Access technology: 'Adaptacaps', syringes
- Training in medication
- Preparatory visits to the clinic
- Cues, reminders, diary cards
- Social and community support
- **Time** from health care workers

MONITORING THE RESPONSE TO TREATMENT

Tests to monitor immunological and viral responses to HAART are becoming less expensive, though still beyond what the public service can afford. There is at least some evidence that clinical response[9,12] is a reasonable proxy for CD4+ counts and viral loads. These findings need to be confirmed by operational research in the southern African setting.

There are as yet no reports in the literature regarding the success of local paediatric programmes, and most have not been running long enough with sufficient patients for analysis.

SUMMARY AND CONCLUSIONS

Current South African government health policy does not permit therapy with antiretroviral drugs in public service hospitals or clinics. Given the size of the AIDS epidemic in South Africa and the very many South African health care workers who have experienced the morbidity and mortality among their patients, it is remarkable and disquieting that there has not been more protest from the medical fraternity against government policy regarding public access to antiretroviral therapy. History will no doubt question the silence of so many.

Health care workers managing HIV-infected children must become more active in gaining access to HAART for their patients. Successful partnerships between foreign donors, local NGOs and public service facilities offer models for projects to pilot HAART for children and to provide experience and training for health care workers.

Complex regimens and problems with adherence are obstacles to the successful use of HAART in children managed in the public service – but can be overcome. A low-price HAART regimen, if it adds complexity to administration, is not necessarily the cheapest option.

Government, health authorities and heads of academic departments must commit sufficient space and human resources to develop paediatric HIV/AIDS services so that they can become viable platforms for the delivery of HAART. Services should be initiated as pilot projects at all levels of health care delivery, so that units in rural areas can develop in partnership with urban and academic services that can support them. Each pilot project should include elements of audit and operational research, so that in the process of implementation, all practice can be measured and assessed as services are delivered.

The cost of a sufficient, dedicated and robust health care service will be significant, but such a service must be established as soon as possible.

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