

Ensuring a Positive Outlook for an HIV-Negative Future: The Role of PMTCT

A Discussion of Key-Findings from the 3rd South African AIDS Conference

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INTRODUCTION

With an ambitious National Strategic Plan on HIV/AIDS for 2007-2011 (NSP) announced in March 2007 and a major roll-out of prevention, treatment and care programmes underway, the tone of the 3rd South African AIDS Conference changed dramatically from previous years. Seemingly able to leave AIDS denialism in the past, a turning point has been reached and South Africa may be able to lead the continent into a new wave of AIDS responsibility.

In this context, the Conference was a forum for discussion of a diverse set of topics related to AIDS, including cutting-edge research and technologies, gender and socio-economic inequalities, community exchange, as well as prevention strategies ranging from voluntary counselling and testing to mass male circumcision programmes.

While the development of a comprehensive NSP was applauded and supported within the Conference Declaration on HIV and AIDS, eyes were also fixed on the future. Linking many of the sessions was the importance of taking stock not only of the issues that the country is currently confronting, but the necessity to look long-term and assess how AIDS will impact society in the future. Dr. Peter Piot, Executive Director of UNAIDS, challenged countries to respond to AIDS in terms of generations, not just years. In South Africa, nowhere is this statement felt more acutely than in the prevention of mother-to-child transmission (PMTCT).

South Africa is one of nine countries with an increasing child mortality rate. In the province of KwaZulu-Natal, this rate has trebled in the past 15 years (Rollins, 2007). Currently, PMTCT is appallingly insufficient, with coverage estimated at 17% by Dr. Glenda Gray of the Peri-natal HIV Research Unit. The overall MTCT rate is approximately 20.8%. Professor Nigel Rollins of the Centre for Maternal and Child Health at the University of KwaZulu-Natal (UKZN) stressed the feasibility of eliminating MTCT with the appropriate goals and strategies in place.

With an objective to scale up coverage and reduce MTCT to less than 5% by 2011, PMTCT is placed at the top the NSP's priority list. Within Conference sessions, reviewed and up for discussion were four areas of PMTCT anti-retroviral therapy (ART) that may prove imperative to achieving NSP targets:

1. The use of preventative treatment, particularly in resource-limited settings;
2. Improvements in breastfeeding strategies by HIV-positive mothers;
3. The development and monitoring of treatment failure, and

4. Access to alternative and second-line treatment regimes. Although the NSP's mass scale-up PMTCT programme is just beginning, each issue must be monitored and addressed to ensure comprehensive treatment strategies and to predict future needs.

1. Preventative Treatment

In the plenary session, "Positive Prevention: What Works?", Professor Seth Kalichman from the University of Connecticut highlighted the important role played by ARVs in the United States and their potential role in South Africa, not only from a treatment aspect, but also to prevent transmission. Ensuring that patients receive the treatment improves their health and has the additional benefit of reducing their risk of transmitting HIV.

A study conducted in Uganda demonstrated that those with decreased viral load, often occurring as a result of ART, also have significantly lower rates of transmission (Quinn, 2001). As such, Professor Rollins emphasised that one of the first steps in minimising MTCT is to identify those pregnant woman with a CD4 count <200 copies/mm³, at minimum, and provide them with appropriate treatment. The WHO notes that ART is a prime opportunity to intervene and assist the prevention of vertical transmission, and should be addressed as part of maternal health as well as a prevention strategy.

When expectant mothers do not require treatment, the WHO guidelines recommend dual ARV therapy. As a minimum requirement for PMTCT, however, WHO suggests single-dose Nevirapine (sdNVP) to be administered to mothers during labour and to the child after birth. Yet, often these guidelines are not met in resource-limited settings. During her plenary session, "Opportunities for Scaling up PMTCT", Dr Glenda Gray presented results of two recent South African PMTCT studies that assessed the effectiveness of alternative PMTCT treatment strategies when optimal guidelines cannot be reached.

The first reported on the safe and effective use of short-course first-line nucleoside analogue regimens (d4T, ddI, d4T+ddI, and Zidovudine (AZT)) for PMTCT from 34 weeks of gestation through delivery, and for six weeks in infants in place of WHO-recommended sdNVP (Gray, 2006). Results demonstrated both a reduction in maternal viral load and in MTCT.

The second revealed that, when women cannot access ante-natal care or HIV testing for sdNVP prophylaxis, post-exposure prophylaxis to the infant may be used as an important preventative strategy (Gray, 2005). This RTC comparing sdNVP against six weeks of AZT within 24 hours of delivery found that, at 12 weeks, fewer infants were found infected with HIV after sdNVP than those treated with AZT. Other factors associated with infection following birth included maternal CD4 cell count, viral load and breastfeeding. These results were echoed with similar findings on PMTCT operational effectiveness across South Africa (Jackson, 2007).

To ensure effective PMTCT and child survival, maternal health must be adequately addressed and integrated with child health. While it is imperative to identify and

provide ante-natal treatment to expectant mothers to enable positive prevention of MTCT, there is also a need to research and recognise a variety of PMTCT treatment options beyond current WHO-recommended guidelines. As the challenges faced in resource-limited settings often require greater treatment flexibility, the NSP must be cognisant of these limitations, and monitor treatment alternatives at various points of peri-natal care to assist in reducing HIV transmission to infants.

2. Breastfeeding

As suggested by the results of Dr. Gray's research, breastfeeding is an important factor associated with MTCT. The Conference Declaration reflects acute awareness that post-natal transmission of HIV via breastfeeding reverses any gains achieved by peri-natal ART interventions. Dr Gray noted that 300 000 infants each year contract HIV through their mother's breast-milk. However, the strategies to combat this major obstacle are less clear and remain controversial.

She referred to a recent study performed in KwaZulu-Natal by Prof Jerry Coovadia and colleagues (2007) which demonstrated infection rates of 14.1% after six weeks, and 19.5% after six months in exclusively breastfed infants. Yet, these exclusively breastfed infants were significantly less likely to acquire infection than were breastfed infants who also received solids and those who received both breast milk and formula milk. Additionally, infant mortality after three months was lower (at 6.1%) in exclusively breastfed infants versus those given replacements (at 15.1%).

The importance of breastfeeding to child survival rates, particularly in resource-limited settings, has prompted recent studies examining the effectiveness of ARV treatment in breastfed infants in reducing transmission. An RTC conducted by Thior and colleagues (2006) found that in preventing post-natal HIV, infection rates were lower in the formula-fed group treated with one month's AZT (5.6%) than those breastfed and also undergoing AZT treatment for six months (9.0%) at both seven and 18 months of age. Yet, similar to Coovadia's study, the cumulative infant mortality at seven months was significantly higher for the formula-fed group.

While breastfeeding combined with ART may not be as effective in preventing post-natal MTCT as exclusive formula feeding, these results also demonstrate the importance of breastfeeding and the risk inherent in formula feeding for infant mortality rates. For example, following current WHO guidelines, where access to acceptable, feasible, affordable, safe and sustainable replacement feeding is not available, the Conference Declaration promotes exclusive breastfeeding for six months. The risk-benefit ratio of maternal breastfeeding must be carefully weighed when developing and promoting infant feeding strategies.

With study results mixed and remaining controversial, further research in ART for pregnant women and their children was urged by Dr. Gray as the only means to minimise breast milk transmission. Emerging research, therefore, warrants continuous review and updating of present UNICEF, WHO and UNAIDS infant feeding guidelines. As such, the role of those implementing NSP policies needs to be bold and proactive, so as to evolve continually with careful monitoring and evaluation of programming, and

incorporating reviews of changes in international guidelines to ensure both improved survival and reduction of HIV transmission rates in infants.

3. Treatment Failure

With increased access to peri-natal ART outlined, the NSP must also anticipate the coinciding increase in treatment resistance. Regardless of treatment adherence levels, ARV resistance is inevitable given HIV's high mutation rate and the requirement for life-long treatment. This requires vigilance when planning to prevent and reduce MTCT rates for the future.

From the National Institute for Communicable Diseases, Dr. Lynn Morris reviewed a recent South African study performed by Marconi (2007) which found that 4% of patients on first-line ARVs experienced virologic failure, with 75.6% having more than one resistance mutation and 53.8% having dual-class resistance. While currently in South Africa resistance presents in less than 5% in all drug classes (predominantly acquired resistance), the level of transmitted resistance will evolve over time as it correlates directly with the level of treatment. Modeling analysis predicts that within the next decade, if 10% of the infected population is on treatment, the country will begin to detect transmitted resistance up to 10% (Blower, 2005). This must be monitored.

Results from a recent article revealed that, of women who received sdNVP for PMTCT with subsequent NVP-based ART initiated within six months, 41.7% experienced virologic failure (Lockman et al, 2007). Similarly, a significant increase in virologic failure developed in infants who had received sdNVP, with 40% expressing baseline resistance mutations. Yet, Dr. Morris also presented study results which found the effectiveness of sdNVP to reduce MTCT was not impaired in subsequent pregnancies, and that NVP-based treatment initiated after a six-month period from delivery indicated no significant treatment failure (Martinson et al, 2007; Lockman et al, 2007). This may indicate that viral resistance from prior exposure to sdNVP may fade with time, and cautions resuming or beginning NVP-based therapies immediately after sdNVP treatment.

Nonetheless, these concerns of treatment resistance have important implications and suggest a need for careful observation of PMTCT treatment and its effects on post-natal ART. Nathan Geffen of the Treatment Action Campaign (TAC), and Fatima Hassan of the Aids Law Project (ALP), suggested that there is a pressing need to introduce dual-therapy PMTCT in provincial guidelines. Currently, dual-therapy is only provided in the Western Cape province, where it has both improved the success rate of PMTCT and reduced the risk of NVP resistance. Building on the success of this programme, there is an urgent call for other provinces to implement similar guidelines, in conjunction with guidelines revised by the WHO, as well as South Africa's Medicines Control Council and Medicines Regulatory Authority.

For the NSP to maximise the returns from a mass scale-up and roll-out of ART and PMTCT strategies, the appropriate guidelines need to be outlined and implemented and the monitoring and evaluation systems need to be in place. This system must not only track ARV treatment regimes and adherence, but also anticipate resistance to therapy. This includes not only a focus on acquired resistance, which is a more immediate issue, but

also the emergence of transmitted resistance. These systems will signal “early warning indicators” on treatment resistance to ensure an effective response in both treating and preventing possible transmission of resistant strains.

4. Treatment Access

As Professor Rollins stressed the need to bridge the gap between ante-natal care and post-natal care, the appropriate treatment for mothers and their infants before and after birth must be integrated and monitored. Additionally, the emerging challenge of treatment failure, particularly with NVP-based therapies after sdNVP for PMTCT underscores the necessity of available second-line treatments.

Striving to place one-million people on treatment by 2011, and with the national ARV tender up for review at the end of 2007, Ms. Hassan emphasised the need for the NSP to think beyond current treatment regimes towards more costly second-line treatments. Confronting the inevitable demand for alternative treatment, ALP's Jonathan Berger declared that, by 2011, price and sustainability of supply will be a major constraint for South Africa.

Dr. Piot echoed this concern in the Satellite session “25 Years from Now ... Will AIDS be the face of South Africa?”, describing the pioneer role that Brazil played as the first developing country to provide free universal access to low-cost generic first-line ART in the public health system. With its successes, however, Brazil has entered a mature phase of the epidemic. As patients have moved to second and third-line ARV treatments within the last two years, treatment costs have doubled. Persevering through the increased treatment costs that have challenged the sustainability of its treatment programme, Brazil serves as an example to other infant national programmes, such as that of South Africa. In these cases, Dr. Piot re-emphasised that long-term planning is necessary to ensure optimal treatment outcomes, by forecasting the needs and associated costs of changing therapy regimes.

In addition to recognising future treatment costs, however, Mr. Berger asserts that the country must ensure a generic market in South Africa to maintain sustainability of the NSP's ARV programme. Generic competition decreases price, increases consistency of supply and allows for fixed-dose combinations, all important for the longevity and effectiveness of a national strategy. In response, the TAC and the ALP are targeting pharmaceutical giants MSD and Abbott in an attempt to eliminate their monopoly on the South African ARV market for Efavirenz (EFV) and heat-stable Ritonavir-boosted Lopinavir (LPV/r), respectively.

EFV is used as replacement treatment for non-pregnant women and children presenting with side-effects to NVP treatment, and LPV/r is used as a second-line treatment when NVP resistance develops. While MSD's price for EFV has declined a dramatic 52.6% to \$237.25 since 2001, the cheapest generic on the international market was priced at \$164 in May 2007. There is currently no generic competitor on the South African market. While MSD has issued a single voluntary licence to South Africa's Aspen Pharmacare, they have neither been able to confirm a competitive price for their product, nor register their product with the Medicines Control Council. Abbott has

refused to license one of the most important second-line treatments - heat-stable LPV/r - and, in so doing, has effectively abolished any competition until patent expiry.

A deficient generic market not only eliminates the possibility for competitive national tenders, but also threatens the availability of fixed-dose combinations and consistent supply. By simplifying multi-drug treatment regimes to a single pill, generic fixed dose combinations not only increase accessibility of ART through reduced costs, but importantly assist to increase adherence rates, and thereby impede resistance. Similarly, drug stock-outs affect the ability to comply with complete treatment regimes and challenge treatment scale-up efforts. Mr. Berger called attention to the stock-outs faced in neighbouring Botswana, with first-line treatments having to be either deferred to a generic manufacturer where possible, or enrollment of any new patients being halted. In South Africa, a similar scenario would place the goals of the NSP in jeopardy.

Considerations for a mass scale-up of second-line treatment must acknowledge the increased demand that will be placed on the supply chain. If there is no generic competitor to provide a relief supply in the case of a stock-out, treatment goals may be impeded. As such, Mr. Berger points to the development of a comprehensive National Drug Policy and the use of international development treaties on access issues - such as the Doha Declaration of 2002, the Gaborone Declaration of 2005 and the International Guidelines on HIV/AIDS and Human Rights of 2002 - to ensure the availability of low-cost generic treatments.

Long term strategic planning in treatment and the use of both national and international policies to address these treatment needs is a crucial element to ensure the viability and sustainability of the NSP. It is imperative that the country can identify appropriate second and third-line treatment for use when first-line treatments fail, and that reliable supply at reasonable costs can be secured.

Conclusion

The 3rd South African AIDS Conference highlighted the necessity to monitor and evaluate treatment programming to assist in the development of long-term strategic plans to address the epidemic nationally. This theme carried and challenged sessions discussing PMTCT treatment and the important role played by ARVs in preventing transmission as part of a multifaceted approach.

Positive prevention, peri-natal and post-natal ARV strategies are all avenues that should be investigated to assist in the reduction of vertical transmission, particularly in environments where the appropriate resources may not be available to provide best-practice PMTCT treatment and care. Transmission of HIV through breast milk and increased infant mortality rates in those receiving replacement feeds requires further research and development, as does the area of first and second-line treatment resistance, particularly to NVP-based treatment regimes.

Finally, with treatment resistance looming, access to appropriate and sustainable second-line treatments must be identified and secured at a reasonable cost. As such, the country and each province must progressively assess and revise their treatment

guidelines. While these research findings may create inspiring advances in MTCT treatment and prevention, many obstacles remain on the ground that must be confronted in order to ensure effective programme implementation.

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