

HATIP

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Recent news

This week's edition of HIV & AIDS Treatment in Practice is a round-up of recent news reports from www.aidsmap.com of particular relevance to HIV treatment in resource-limited settings.

It also includes our reports on the recently-announced Thai HIV vaccine study.

We'd like to draw attention to a number of recent studies that report **on training, capacity-building and evaluation of services**. As services scale up, this form of operational research is becoming more abundant –and more important.

For example, we cover a report from a research group in South Africa, which evaluated the extent to which staff in primary health clinics in a rural area were following IMCI guidelines for screening infants to identify those who required further investigations for HIV infection. The study showed that many infants who required further investigation were being missed, with potentially serious consequences. Getting interventions like this right are a basic step in scaling up diagnosis and treatment of children, and this article should be essential reading for anyone trying to improve treatment for children with HIV.

Two companion reports on task-shifting in Uganda show that while non-physicians are in general doing well at identifying which adult patients are eligible for HIV treatment, non-physician subscribers in Uganda felt they needed a lot more training. Two out of five non-physicians who were already involved in providing ART said that they had received no training in initiating patients on ART., perhaps an indication of the extent to which human resources are stretched to the limit as demand for ART continues to grow.

We also highlight a study of ART provision within antenatal clinics in Zambia, which shows that uptake of ART among eligible pregnant women doubled when women no longer had to attend separate clinics to receive antenatal care and antiretroviral treatment. This is one of many basic steps in integrating care that we will be reviewing in more detail in future editions of HATIP.

Training and capacity-building

Clinical officers and nurses make similar decisions to physicians on starting antiretroviral therapy in rural Uganda

By Roger Pebody & Carole Leach-Lemens

An analysis of decision-making by non-specialist physicians, clinical officers and nurses in Uganda has found that there is a high level of agreement in decisions on starting antiretroviral therapy.

The study, in the journal *Human Resources for Health*, contributes to the evidence base in support of task-shifting, and may ease concerns about a decrease in quality compared to current standards of care. It lends support to arguments for increased investment in training of nurses and clinical officers for the delivery of antiretroviral therapy in rural and semi-rural settings.

Rapid scale up of antiretroviral therapy has brought to light weaknesses in the health systems of developing countries. WHO

estimates that over four million health workers are needed, and this shortage of medical doctors and other health workers trained to deliver HIV treatment and care has been identified as the most serious barrier to the sustained scale up of ART in resource-poor settings.

Task-shifting involves the delegation of healthcare tasks from more highly trained individuals to those with less training, and it has been increasingly employed as a way to help address the shortage of highly trained staff in many resource-limited settings.

Few countries in the developing world legally mandate non-physician clinicians to provide HIV treatment and care (exceptions include Malawi, Kenya, Ethiopia and Uganda). There is a reluctance to legalise task-shifting due to concerns about the capacity of the workers, as well as the quality of care provided.

Conversely this is a common and very successful practice in the developed world where non-physician clinicians (in particular nurse practitioners) play a central role in the treatment and care of HIV-positive patients.

Moreover the Integrated Management of Adolescent and Illnesses (IMAI) guidance, developed by the World Health Organization and partners, uses task-shifting to support a public health approach to treating HIV within government health systems. The target audience is principally healthcare workers providing clinical care at front-line health facilities. More than 30 countries, mostly in sub-Saharan Africa are currently using IMAI.

Ashwin Vasan and colleagues designed a study in which a non-physician first assessed the patient and made a recommendation on whether to start treatment, after which a physician repeated the procedure (without being aware of the initial recommendation). The study compares each worker's assessment, although all final clinical decisions were made by the physician.

Study sites were twelve district hospitals and subdistrict primary care clinics in Uganda. Sites were chosen based on their large HIV programmes, and staff were trained in the management of HIV through the Ministry of Health programme (an adaptation of generic WHO/IMAI protocols). Rural or semi rural sites were chosen to provide an accurate picture of decentralised ART care. Viral load testing was not available and access to CD4 cell counts was limited at all sites.

Healthcare workers were classified as:

- Physicians: those who had completed a six year medical school programme plus a one-year internship. Physicians were not usually HIV specialists.
- Clinical officers: those who had completed three years' pre-service education plus two years' internship.
- Nurses, who had completed between one and four years' formal nursing education.

The authors acknowledge that the variation in the level of training of Ugandan nurses is a limitation of the study. Moreover, the study did not record the number of years of work experience that each worker had.

The researchers used Kappa analysis to evaluate levels of agreement. Kappa is a statistical measurement of the degree of agreement between two observers, and which rates strength of agreement as 'slight' (0 to 0.2), 'fair' (0.2 to 0.4), 'moderate' (0.4 to 0.6), 'substantial' (0.6 to 0.8) or 'almost perfect' (0.8 to 1).

The 521 eligible patients were HIV-positive adults not currently on treatment.

Each patient was first assessed by either a clinical officer or a nurse, and then by a physician. The primary outcome in the study was the final recommendation on whether or not to start antiretroviral therapy.

In the clinical officer arm, agreement with physicians on starting therapy was almost perfect (Kappa 0.91), with 95% of decisions being the same (as opposed to 43% agreement which could be expected by chance alone).

Agreement between nurses and physicians was less consistent and was calculated to be at the top end of the moderate category (Kappa 0.59). A total of 78% of decisions were in agreement, as opposed to 46% which could be expected by chance alone.

Moreover, both nurses and clinical officers were both somewhat more likely than physicians to recommend an alternative to the standard d4T/3TC/nevirapine regime.

Nurses' assessments of patients' WHO clinical stage and TB status were both in substantial agreement with those of physicians. On the other hand, the assessments of clinical officers for both these items were only in moderate agreement with the doctors.

On a number of items, the agreement of both nurses and clinical officers with physicians was assessed as 'fair'. This was the case for functional status (able to work, able to walk, etc.), opportunistic infection status, absolute exceptions to starting antiretroviral therapy immediately, and patient readiness to start therapy. However the authors note that a number of these variables are subjective in nature. Moreover in some cases there was a great deal of missing data.

Although nurses had higher agreement scores on some items than clinical officers, the authors focus their conclusions on the latter group because of the decisions concerning initiation of therapy. They say that there is "compelling evidence" that clinical officers should be allowed to initiate therapy.

The authors believe that their findings show that under routine conditions at rural health facilities, and without any targeted increase in training or supervision of healthcare workers beyond the national framework, there is agreement in the clinical judgement between different cadres of healthcare workers in terms of starting antiretroviral therapy.

Nonetheless, they also describe the study as a pilot, and argue that "these preliminary data warrant more detailed and multicountry investigation".

Reference

[Vasan A et al. Agreement between physicians and non-physician clinicians in starting antiretroviral therapy in rural Uganda. *Human Resources for Health* 7:75, 2009.](#)

Uganda survey shows major ART training gaps for non-physicians

By Carole Leach-Lemens

A survey of health facilities providing antiretroviral treatment in Uganda has found that nearly two-thirds of those providing ART are not doctors, and report major gaps in training. Two out of every five of this group had received no training in starting patients on ART and two-thirds had not been trained in how to monitor patients on ART.

The findings were published in the August 23 edition of *Human Resources for Health*.

In self-assessment questionnaires seven percent of doctors, 42% of clinical officers, 35% of nurses and 77% of midwives thought their overall knowledge of ART was lower than "good".

Task-shifting from physicians to nurses and clinical officers requires ongoing integrated trainings to ensure the correct use and monitoring of ART if toxicity and drug resistance are to be avoided and the success achieved to date in the management of HIV is to be maintained in resource-poor settings.

Access to ART continues to expand beyond urban centres into remote areas and task-shifting is widely acknowledged as a means to counter the challenge that the chronic shortage of healthcare personnel in resource-poor settings presents. Studies have demonstrated that in some circumstances the quality of care provided by non-physician clinicians is equal to or better than that provided by clinicians.

The Infectious Diseases Institute (IDI) at Makerere University, Uganda together with the (Ugandan) Ministry of Health undertook a training needs assessment that focused on two of the World Health Organization's recommendations for task-shifting in the promotion of access to HIV and other health care services:

- Recommendation Four: countries undertake or update a human resources analysis on the extent to which task-shifting is already taking place and
- Recommendation Nine: countries adopt a systematic approach to harmonised, standardised and competence-based training that is needs-driven and accredited.

A survey of health professionals and heads of antiretroviral therapy clinics from a stratified random sample of 44 of the country's 205 accredited health facilities was undertaken. Six out of 12 catchment areas were chosen by a lottery method. The sample included six regional referral hospitals, 16 district hospitals and 22 health centres. Facilities were grouped as follows: ownership (government or non-governmental organisation and/or faith-based) and whether antiretroviral therapy was being provided.

A sample of health professionals was chosen in collaboration with the head of the ART clinic. Criteria included being present on the day the study team visited. Efforts were made to have at least one doctor, one clinical officer, one nurse and one midwife from each clinic.

Data collection involved self-administered questionnaires for individual health professionals and face-to-face interviews with the heads of the antiretroviral clinics.

Forty-three of the 44 facilities selected were included of which 38 provided ART and five (one district hospital and four health centres) did not.

Expansion of ART from urban clinics to district hospitals and primary care facilities is reflected in the numbers. Although regional referral hospitals provided ART to a higher proportion of people with HIV (45%) than district (33%) and health centres (17%) the authors suggest that over time these percentages may even out as care is transferred closer to accredited facilities near the patient's home.

The sample comprised 265 clinicians: 34 doctors, 46 clinical officers, 124 nurses and 61 midwives. This distribution across professions was markedly different to the distribution of staff at ART clinics. Doctors were under-represented at all facilities, whereas nurses were over-represented at health centres and underrepresented at regional referral and district facilities. ART clinics at two district hospitals and two health centres had no doctors on staff.

ART tasks were performed by all staff interviewed. 64 percent of clinicians prescribing ART were clinical officers, nurses and midwives. The authors note that this task-shifting was in line with recommendations from experts and may well have contributed to increased access to ART.

The study revealed that training on starting and monitoring ART has not kept pace with task-shifting. Of those prescribing ART 35% had not been trained on starting ART and 49% had not been trained on the monitoring of ART. These percentages differed across health professions: 27% of doctors had no training on monitoring ART compared to 64% of other clinicians. Similarly 24% of doctors had

no training on starting ART compared to 38% of clinical officers, 38% of nurses and 49% of midwives.

While higher percentages of doctors and clinical officers attended training on monitoring of ART and paediatric HIV care than nurses and midwives, a lower percentage of doctors and clinical officers attended training on voluntary counselling and testing than nurses and midwives.

Self-assessment of knowledge of ART also differed across professions and was closely related to training in starting and monitoring ART: Ratings were categorized as "excellent", "very good" and "good" and were grouped together as "sufficient". 75% of all respondents deemed their overall knowledge of HIV as sufficient and 40% rated their overall knowledge of ART as sufficient. 7% of doctors prescribing ART rated knowledge less than "good" compared to 48% of other clinicians.

Limitations noted by the authors include overrepresentation of certain professionals at some facilities and underrepresentation of others due to reliance on those present at accredited ART clinics on the day of the study.

The authors further note that of the 45 facilities in the sample two remote facilities were replaced by those easier to reach. Task-shifting and an absence of training, the authors believe, were more likely to occur in remote facilities so the sample may have underestimated the extent of task-shifting in addition to the associated ART training needs.

The authors suggest that this assessment provides an innovative method that can be replicated to inform ART trainings in the context of ongoing scale up and task-shifting. The authors conclude that "Training initiatives should be an integral part of the support for task-shifting and ensure that ART is used correctly and toxicity or drug resistance does not reverse the successes to date."

Reference

Lutalo IM et al. *Training needs assessment for clinicians at antiretroviral therapy clinics: evidence from a national survey in Uganda*. Human Resources for Health 7:76, 2009.

Nurse prescribing of ARVs: evidence of success in Rwanda and Lesotho

By Keith Alcorn

Nurses in Rwanda and Lesotho are successfully prescribing antiretroviral drugs and managing HIV treatment, two studies published this month show.

Both Rwanda and Lesotho face a serious shortage of doctors, and in order to increase the capacity of the health system to treat people with HIV the World Health Organization recommends "task shifting"—the delegation of many medical tasks including ARV prescription and management to nurses and clinical officers.

Some countries have been quicker than others to adopt task-shifting as a means of increasing capacity. In some countries, such as South Africa, the policy remains controversial [despite the existence of legislation](#) that permits nurse-prescribing.

Task shifting in Rwanda

In September 2005, Rwanda launched a pilot programme of task shifting. One nurse in each of three rural primary health centres was trained to examine patients with HIV and prescribe antiretroviral therapy (ART) in simple cases (complex cases were referred to a doctor). Nurses had to complete at least 50 consultations with patients eligible for ART under the observation of a doctor before being allowed to treat patients independently.

The new study, by Fabienne Shumbusho (Family Health International, Kigali, Rwanda) and colleagues, [published in PLoS Medicine](#), evaluates the success and safety of the programme.

Shumbusho and colleagues reviewed the medical records of 1,076 patients enrolled in the programme between September 2005 and March 2008. They examined whether the nurses had followed national guidelines on ART prescription and monitored the patients correctly. They also looked at patients' health outcomes, such as their death rate, changes in body weight and CD4 cell count (a marker of how healthy the patient's immune system was), and whether patients maintained contact with caregivers.

The researchers found that by March 2008, 451 patients had been eligible for ART, of whom 435 received treatment. None of the patients were prescribed ART when they should not have been. Only one prescription did not follow national guidelines. At every visit, nurses were supposed to assess whether patients were taking their drugs and to monitor side-effects. They did this most of the time (in 89% of clinic visits, nurses assessed adherence, and in 85% of visits they assessed side-effects).

By March 2008, 390 (90%) patients were alive on ART, 29 (7%) had died, only one (under 1%) was lost to follow-up, and none had stopped treatment. Most patients gained weight in the first six months and their CD4 cell counts increased.

Outcomes, including death rate, were similar to those from the doctor-led Rwandan national ART program and other African national doctor-led programmes.

The study, say the authors, "demonstrates the feasibility and suggests effectiveness of nurse-centred task shifting for decentralised ART services without compromising the quality of care."

But there are also several limitations to the study, which the authors discuss in their paper. For example, the authors say that they did not directly compare outcomes from this nurse-centered model of care with those from traditional physician-centered models. This makes it difficult to ascertain if patients' outcomes were as a result of the nurses' role or due to doctors' intensive supervision.

Task shifting in Lesotho

Médecins sans Frontières reported two-year outcomes from a nurse-driven antiretroviral treatment programme in the Scott district of Lesotho, a very poor country with one of the most severe shortages of doctors in sub-Saharan Africa. Lesotho has just five doctors per 100,000 inhabitants, most of them visiting foreigners, compared to 74 doctors per 100,000 inhabitants in South Africa.

MSF began providing antiretroviral treatment in partnership with the Ministry of Health in the Scott district, a mountainous rural area with a population of around 200,000, using a nurse-driven model of care supported by community health workers. Nurses are also in very short supply in Lesotho due to the attraction of higher wages in South Africa and attrition due to AIDS.

The model of care is described in full in a paper [published in the Journal of the International AIDS Society](#), which is freely accessible. In brief, one or two nurses provide care at each of the 14 health centres, and receive a supervisory visit once every week or two from a doctor or nurse clinician.

Nurses began prescribing ART after intensive in-service training, as well as quarterly training based on the World Health Organization's Integrated Management of Adolescent and Adult Illness guidance.

Soon after the introduction of ART in 2006 it was discovered that nurses were seeing up to 45 patients a day, and in order to relieve their workload a cadre of paid lay counsellors, predominantly people

living with HIV, was recruited in order to carry out pre-treatment counselling, defaulter tracing and clinic organisation.

By July 2009 13,243 patients had been enrolled on ART, and 76.5% of patients still remained in care after two years, compared with an African average of 61%.

The service has also been successful in retaining children in care, and providing antiretroviral treatment without paediatric specialists, but the number of children receiving treatment remains small – 116 in 2008 – despite the fact that 56% of deaths in children in Lesotho are estimated to be HIV-related.

MSF is now in the process of handing over the programme to the Ministry of Health.

The authors highlight a number of ongoing challenges for task-shifting in the programme:

- How to increase nurse confidence and skills in paediatric care?
- How to increase the role of lay counsellors in screening stable patients on ART without compromising the standard of care?
- How to sustain the high rate of enrolment on treatment without compromising the quality of care?
- How to improve diagnosis and management of TB?
- How to retain staff, maintain staffing levels and ensure adequate supervision and clinical mentorship?
- How to scale up the use of lay counsellors at the national level while ensuring consistent policy and standards?

Nevertheless the authors conclude that experience in Lesotho shows that “HIV care and treatment can be provided effectively at the primary care level,” while validating the approach of task shifting in several areas, including paediatric treatment and lay counsellor-supported adherence and case management.

Three editions of [HIV & AIDS Treatment in Practice published in 2008](#) reviewed recent successes and challenges in task shifting.

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Cohen R et al. *Antiretroviral treatment outcomes from a nurse-driven, community-supported HIV/AIDS treatment programme in rural Lesotho: observational cohort assessment at two years*. J Int AIDS Soc 12: 23, 2009. doi:10.1186/1758-2652-12-23

People with HIV providing high quality treatment support in community

By Mara Kardas-Nelson

A study conducted in rural Kenya demonstrates that task-shifting HIV treatment programmes from clinic staff to community health workers, specifically those living with HIV, is both feasible and acceptable, giving support for further exploration of this model and providing alternatives to the physician-centred approach.

The two-year long study, published in the September edition of the *Journal of the International AIDS Society*, was conducted by American and Kenyan investigators at a United States Agency for International Development-Academic Model Providing Access to Healthcare (USAID-AMPATH) Partnership clinic in central Kenya.

Task-shifting has been advocated by the World Health Organization and other health experts in the context of a clinical health care worker shortage in resource-limited settings.

The study evaluates a community care coordinator (CCC) model, in which HIV-positive care workers provide support for their clinically

stable HIV-infected peers with the assistance of personal digital assistants (PDAs). Results show clinic visits being reduced by 50% among the intervention group and accepted by clinic staff, patients, and CCCs themselves. CCCs were also able to identify patients' psychosocial problems and monitor treatment adherence.

The USAID-AMPATH Partnership clinic Mosoriot Rural Health Centre, located in the rural Kosirai Division of Kenya, was the site of the study. Eight of the 24 sub-locations of the Kosirai Division were randomly assigned to the intervention, with the rest acting as controls.

Nine HIV-positive patients from the Mosoriot clinic were selected to be CCCs, underwent didactic and practical training, and were paid an outreach worker's salary, lower than that of clinical staff. Eight entered the field, with one acting as an alternate. All eight remained in the field for the duration, managing between eight and 20 patients each.

In the CCC model patients were seen every three months at the clinic rather than monthly as occurs in the Mosoriot standard of care model.

During the two-month interim, patients would be visited monthly by their CCC, who measured their vital signs and reviewed symptoms as guided by a preprogrammed PDA: CCCs would ask patients a series of questions regarding their health, such as the existence of a cough or vomiting, and record answers in the PDA. If a patient displayed a symptom or collection of symptoms, the device prompted further questions, such as their length and severity, and triggered an alert if patients' answers fell outside of pre-established parameters, giving detailed instructions to CCCs for further action. CCCs also dispensed patients' monthly supply of ART and opportunist infection medication.

CCCs underwent continuous evaluation and assessment throughout the study - more rigorously during the mentoring period - and were given superior, satisfactory, or unsatisfactory evaluation scores by clinical officers.

At the end of the first year, 133 formal evaluations had been completed on the eight active CCCs (16 to 17 evaluations per CCC). CCCs consistently received superior summary scores: 89% of all summary scores were superior and the remaining satisfactory. 88 evaluations (11 per CCC) were undertaken in Year 2, during which 94% of summary scores were superior. Clinic staff also monitored CCC performance by comparing data collected at home visits, including that recorded in PDAs, with data collected at the clinic.

Investigators used evaluations and transcripts of monthly CCC meetings to assess the model, highlight and address problems, and improve the programme throughout the study. Investigators also regularly met with CCCs and clinical officers to discuss barriers and enhance CCC performance.

At the trial's end, of those not lost to follow-up, 64% (56 of 87) of patients in the intervention arm and 52% (58 of 103) in the control arm were willing to continue ($p = 0.26$). Additionally, CCCs were contacted by non-enrolled patients who wanted to receive such care. As such, investigators claim that patients accepted the programme.

In addition to reducing patient visits, the CCC model resulted in greater identification of and support in resolving psychosocial issues, such as alcohol abuse and food insecurity, than in the standard of care model. CCCs themselves also felt that they were better able to monitor treatment adherence than clinic staff as pills could be less easily hidden during home visits. Finally, CCCs acted as a link between the AMPATH pharmacy, outreach and clinical teams, and patients.

The author's warn that such a programme is not cost free. Training, PDAs, and salaries must be accounted for, but may be partially offset by the decrease in clinic visits.

Additionally, HIV disclosure remains an issue for patients, and therefore similar programmes should aim to avoid the "AIDS label."

It took longer than anticipated for CCCs to adapt to new technologies such as PDAs, and therefore more time should be given to training with such instruments; and mechanisms must be put in place to facilitate CCC referral to the clinic and clinic referral of follow-up of particular issues to the CCCs.

Issues such as stigma and client and staff expectations were highlighted and addressed throughout the study's period. The authors also stress the importance of finding committed individuals to act as CCCs.

Reference

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Mothers and children

Water treatment does not reduce diarrhoea in infants born to Kenyan mothers with HIV

By Carole Leach-Lemens

Further evidence that the provision of clean water is not enough to prevent weaning-associated diarrhoea among infants born to HIV-positive mothers who are weaned early in resource-poor settings was presented in a study by Julie Harris and colleagues in the September 16th edition of *The Journal of Infectious Diseases* with an accompanying editorial by Louise Kuhn and Grace Aldrovandi.

Access to clean water is a major public health concern in resource-poor settings, and is of particular concern for the survival of children. Diarrhoea is one of the top three leading causes of infant mortality in these settings.

Interventions to improve water quality and hygiene practices have been introduced to help reduce the high rates of infant mortality. Kuhn and Aldrovandi stress that this takes on special significance for maternal HIV infection, where in the hopes of preventing HIV transmission the majority of women with HIV in resource-poor settings choose either not to breastfeed or else wean early.

While breastfeeding accounts for up to half of all cases of mother-to-child HIV transmission, shortening the duration of breastfeeding and substituting replacement feeding has resulted in [increased or equal rates of infant mortality](#) when compared to exclusive breastfeeding, as well as [higher rates of diarrhoea and gastroenteritis](#).

Mixed feeding, in which infants are exposed to breast milk and to other liquids, as well as solid food and formula feed or cow's milk, is associated with a higher rate of HIV transmission, probably due to exposure to allergens that irritate the gut and lead to inflammation, thus increasing the risk of HIV infection from breast milk.

[The Zvitambo study](#), published in 2005, showed that infants who received mixed feeding were four times more likely to become infected by six months of age than infants who were exclusively breastfed.

Such increases are believed to be the result of reduced transmission of protective maternal antibodies, as well as increased

exposure to contaminated water and complementary weaning foods.

In response to these outcomes the World Health Organization recommends exclusive breastfeeding for six months followed by rapid weaning if subsequent replacement feeding is affordable, feasible, available, safe and sustainable (AFASS) to reduce HIV transmission from mother to child. If not, then the recommendation is to continue breastfeeding beyond six months.

The water safety study

Begun in July 2003, the Kisumu (Kenya) Breastfeeding Study (KiBS) was a clinical trial designed to evaluate if antiretroviral treatment during the six-month postpartum period helps to prevent the transmission of HIV through breastfeeding.

Provision of antiretroviral treatment began during pregnancy and continued for the six months following delivery. Infants were given a single dose of nevirapine within 72 hours of birth. Women were encouraged to exclusively breastfeed for 5.5 months and then rapidly wean their infants from breast milk by six months of age (within two weeks). Preliminary results indicated that ART was highly effective.

However, 18 months into the study routine safety monitoring discovered higher than expected rates of diarrhoea among infants after weaning. Enrolment stopped and the data were reviewed.

To address the issue a household-based water quality intervention, Safe Water System (SWS), was introduced. Field workers provided mothers in the KiBS cohort with safe water storage vessels, instructions on food and water hygiene and on washing their hands with soap, and sodium hypochlorite (WaterGuard) for household water treatment. Instruction and replacements as needed were provided on an ongoing basis at no cost.

In field trials, the use of SWS has resulted in 25 to 85% reduction in the risk of diarrhoea. The World Health Organization recommends its use for people living with HIV and their households.

The authors compared incidence of diarrhoea in infants enrolled prior to the intervention from August 2003 to March 2005 (cohort A) and in a second cohort enrolled from August 2005 to January 2007 (cohort B).

Routine clinic and home visits were scheduled, beginning at one week of age at home and two weeks of age at the clinic, and then alternating week by week until 48 weeks of age. Free care was provided and all travel expenses reimbursed. Mothers were encouraged to bring their infants for medical attention as needed. Stored water was tested regularly from November 2006 to November 2007 for the presence of chlorine to indicate adherence to recommended SWS use.

A total of 234 cohort A infants and 257 cohort B infants were included in the analysis. Over 90% of the households in both cohorts had access to water supplies other than surface water.

230 infants from cohort A were included in the diarrhoea analysis and 252 from cohort B. Most infants did not have clinic visits for diarrhoea during the exclusive breastfeeding period, the weaning or post-weaning period.

However, frequency of clinic visits was highest during the weaning period in both cohorts. Sixteen per cent of cohort A infants and 16% of cohort B infants had ≥ 1 clinic visit for diarrhoea ($P=0.89$) during this month.

The introduction of SWS did not decrease the risk of diarrhoea among infants of HIV-infected mothers during this time of rapid and early weaning in spite of high adherence rates.

While there is limited understanding of the causes of infant diarrhoea, the authors note studies have indicated weaning as a risk factor. In addition other studies, the authors stress, have shown

how both exclusive and non-exclusive breastfeeding are protective against severe diarrhoea.

Crucially breastfeeding, they argue, protects infants not only from exposure to bacteria found in water and food but also confers important protective immunologic benefits to fight illness as well as respiratory infection.

Louise Kuhn and Grace Aldrovandi note contaminated water is unlikely to be responsible for the latter and "further supports the idea that breastfeeding protects less by keeping the germs out and more by putting the good stuff in". Weaning foods have been shown to contain bacteria, but many children with diarrhoea show no evidence of bacterial infection, suggesting that change of diet in itself is sufficient to cause serious diarrhoea.

In addition the authors note stopping breastfeeding has been associated with high rates of diarrhoea among infants of both HIV-positive and negative mothers. There are no known differences in the immunologic quality of breast milk in HIV-positive and negative mothers.

The authors note that while the risk of diarrhoea was similar in both cohorts at weaning, the risks before and after weaning were significantly lower in cohort B than in cohort A. They believe that greater exposure to exclusive breastfeeding in cohort B before weaning may have conferred additional protective benefits. SWS during non-weaning periods may also have reduced risk.

The authors suggest that a randomised controlled trial of the effectiveness of SWS on diarrhoea in rapidly weaned infants might provide further insight into its effectiveness in this age group.

Limitations cited by the authors include possible differences in the two cohorts due to one preceding the other by almost two years. Laboratory data on the causes of diarrhoea might have been helpful in better understanding the routes of transmission. The ability to appropriately assess the effect of SWS was limited as the study was not designed to determine the risk factors for transmission of diarrhoea in infants. And, data on SWS adherence was incomplete due to lateness of protocol approval.

An accompanying editorial by Louise Kuhn and Grace Aldrovandi supports the findings of the study that early weaning increases the risk of diarrhoeal disease among infants of HIV-positive women and underscores the importance of the protective benefits of breastfeeding.

Safe water interventions within this specific context can be beneficial, but as an addition to breastfeeding and not as a replacement, they argue. They stress the limitations of some public health interventions as revealed by the authors and note that few safe water interventions have focused on children under the age of one year and none on children not being breastfed. "Children are not little adults", they caution.

Kuhn and Aldrovandi support the authors' conclusion "that further investigation of extended maternal antiretroviral therapy is needed to address the longer duration of breastfeeding required in pathogen-rich environments".

However, they add that in terms of proof of concept the capacity of extended maternal ART and extended infant prophylaxis to prevent HIV transmission after delivery has been demonstrated already. This also presents a means of decreasing the risks of HIV transmission through breast milk while retaining its benefits.

The problems associated with early weaning, known for many years among infants of uninfected women, will now they hope be rediscovered among infants exposed to HIV. This fact, they believe, provides an added incentive to make antiretroviral therapy available for all pregnant and lactating HIV-positive women.

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Screening tool for HIV in children not being used effectively by health care workers

By Carole Leach-Lemens

Incorrect use in routine practice of a World Health Organization (WHO)/UNICEF HIV screening tool for children at primary health care clinics in Limpopo and KwaZulu Natal provinces, South Africa, leads to the failure of life-saving interventions, Christiane Horwood and colleagues reported in a study in the September 22 2009 edition of *BMC Pediatrics*.

Forty per cent of trained health workers failed to identify HIV in any child and not one was able to classify every child correctly for HIV.

In South Africa where HIV prevalence rates among pregnant women remain at 29%, the burden of paediatric HIV disease continues to grow. Limpopo – with a mostly rural population of 5.5 million – has high rates of poverty and poor access to basic services. While KwaZulu Natal has less poverty, half of the 10-million-strong population lives in rural areas and antenatal HIV prevalence in 2006 was close to 40%.

Insufficient testing and follow-up of HIV-exposed children leads to high mortality rates with over half of untreated children dying within the first two years of life. Few children who need antiretroviral treatment receive it in spite of it being free. Improved follow-up of HIV exposed children, increased early identification of children with symptomatic HIV and improved access to ART for children are urgently needed.

New guidelines from WHO recommend that, where virological testing is unavailable, children should be started on antiretroviral treatment based on clinical diagnosis alone followed by quick confirmation of HIV status.

WHO and UNICEF developed the Integrated Management of Childhood Illnesses (IMCI) strategy to improve child survival in resource-poor settings. Focusing on the well-being of the whole child, the aim is to reduce death, illness, disability, and to promote improved growth and development among children under five years of age. South Africa adopted these guidelines as the standard of care for children at the primary level in 1997.

Multi-country evaluations of the IMCI strategy indicate, when used correctly, improved health worker performance and quality of care as well as a reduction in under-five mortality and improved nutritional status.

The guidelines have been adapted to incorporate a validated HIV component (including an algorithm) to identify and manage HIV-infected (at risk for early death) and exposed (symptomatic) children. The IMCI course includes comprehensive training on this component.

For effective use of the algorithm, healthcare workers are expected to ask every mother bringing a sick child to a healthcare facility whether she has been tested for HIV, so that children may be classified as HIV-exposed, and all children should be assessed for clinical symptoms suggestive of HIV. The presence of three or more symptoms should trigger further investigation and the carer should be advised of the need for the child to be tested for HIV.

In this first known evaluation of the IMCI/HIV guidelines, the study was designed to show how the guidelines are used by IMCI trained health workers, the validity of the HIV algorithm when used by expert IMCI practitioners in routine practice and the burden of HIV disease among under-fives attending primary health care facilities in Limpopo and KwaZulu Natal provinces.

Between May 2006 and January 2007 seventy-seven randomly selected IMCI trained health workers were observed by IMCI experts in 74 primary health care facilities in Limpopo and KwaZulu Natal provinces.

All sick children between the ages of two months and five years were eligible. Consultations with a total of 1357 sick children were observed. A different IMCI expert reassessed each child to confirm correct findings.

Consent for HIV testing for all children who attended was requested from parents or legal guardians. Positive rapid tests were confirmed with HIV polymerase chain reaction (PCR) tests in children under 18 months of age. HIV-positive children had CD4 counts and HIV clinical staging done.

Each health worker was observed for a mean of 2.2 days and 17.7 consultations. The average age of the observed children was 19.6 months, of whom 40.7% (552) were under one year of age. A third of all consultations were observed in Limpopo and the remaining two-thirds in KwaZulu Natal.

Of the 1064 children with available HIV test results, 76 tested positive giving an HIV prevalence rate of 7.1% (CI: 5.7 to 8.9%) among children in primary healthcare clinics. Of these 76, one was on antiretroviral treatment. Following CD4 counts or, if unavailable, WHO clinical staging, ART was indicated for 84% (63 of 75) of the remaining children.

When compared to the HIV test results, IMCI experts skilled at using the HIV algorithm correctly identified 90.8% (69 of 76) of HIV-infected children as either suspected symptomatic HIV or HIV-exposed and therefore in need of further investigation. This shows that when used correctly the HIV algorithm is an effective screening tool and can lead to improved access to life-saving treatment for HIV infected and exposed children.

In comparison, over 40% of IMCI-trained health workers failed to identify HIV in any child because of poor or incomplete use of the HIV component. And nine did not classify the disease stage of any child with HIV correctly.

Even when health workers classified children with suspected symptomatic HIV, the need for testing, cotrimoxazole prophylaxis and feeding advice was only communicated to 64%, 31% and 43% of carers, respectively.

The authors suggest several reasons for poor use of the algorithm:

- Inadequate training
- Lack of a clear understanding that the HIV algorithm is a screening tool and not a diagnostic test. IMCI training must clearly explain that most children will test negative and provide appropriate counselling messages. Even with a sensitivity of over 90% in this high-prevalence population it has a low positive predictive value (PPV) which would be lower still when used in low-prevalence settings
- Poor use of the algorithm may be reflective of an overall poor use of IMCI due to: heavy workloads, lack of time for consultation, absence of clinical supervision and support
- Poor application of prevention of mother-to-child transmission (PMTCT) programmes. Even though many mothers reported testing positive, few HIV-exposed children had been tested and most clinics did not test children under five. 73% of mothers had

been tested for HIV, of whom 24% (221) tested positive. Of the 221 HIV-exposed children, only 35% (78) had been tested for HIV within routine services.

The authors recommend the strengthening of PMTCT and linkage with IMCI as well as improved access to HIV PCR for exposed children. This may reduce the need for the algorithm to identify symptomatic HIV. However, it will remain important for children whose mothers do not disclose their status or become infected during pregnancy and breastfeeding, and in settings where virological testing is not available.

The authors note that these findings show that undiagnosed HIV infection is common in primary healthcare clinics among under-five year olds and most have advanced disease. Current recommendations suggest that antiretroviral treatment is begun in children under one year of age as soon as HIV status is confirmed. They also note that their findings support the IMCI recommendation to check all children for possible HIV infection.

The authors highlight the study's strengths. The IMCI experts were all highly experienced and provided a "reliable gold standard"; observation of large numbers of children and health workers made it possible to describe performance using the health worker as the unit of analysis. Health workers had no notice of the observation and observation of large numbers over several days reduced bias.

The authors note several limitations. The observer's presence may have influenced performance and led to bias. For example, health workers may have worked out what to do during the observation. Evaluation of individual ability to identify specific signs did not take place to avoid interference during the consultation. Evaluation of the sensitivity of HIV rapid tests in children under 18 months of age remains incomplete. They did not get CD4 results for all HIV-infected children.

The authors conclude that IMCI and the correct use of the current guidelines can identify HIV-infected and exposed children and provide increased and earlier access to care in South Africa to reduce under-five mortality.

However, poor use of the guidelines limits its potential. The authors suggest further study to understand poor health worker performance "to provide evidence-based interventions to address poor IMCI implementation".

Reference

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ART offer at antenatal clinics doubles uptake in Lusaka

By Carole Leach-Lemens

Integration of antiretroviral treatment into public sector antenatal care (ANC) clinics in Lusaka district, Zambia, more than doubled the percentage of treatment-eligible pregnant women starting antiretroviral treatment before delivery when compared to referral from ANC clinics to antiretroviral clinics, reported William P. Killam and colleagues in a study published in the advance online edition of *AIDS*.

Forty-four percent of women eligible for antiretroviral treatment enrolled within 60 days of HIV diagnosis in the integrated programme compared to 25% who enrolled in separate ART clinics (the control group).

Thirty-three percent of women in the integrated programme began antiretroviral treatment compared to 14% in the control group.

The World Health Organization (WHO) reports an estimated 45% of pregnant HIV-positive women in low- and middle-income countries are receiving antiretroviral treatment, a third of whom get single-dose nevirapine, the least effective form of preventive treatment. Twenty-one percent of pregnant women received an HIV test in 2008. Only a third of those who tested positive were assessed to determine if they needed ART for their own health.

WHO recommends the provision of triple drug combination regimens to treatment-eligible HIV-infected women to protect both their infants from HIV infection and reduce maternal morbidity and mortality. Antiretroviral therapy is recommended for all with CD4 counts below 200 irrespective of symptoms and for people with WHO stage 3 HIV disease if the CD4 count is below 350.

In Zambia as in other parts of the region the presence of public sector antiretroviral clinics does not guarantee that all treatment-eligible pregnant women will actually use them after referral. Prior to this study, less than three percent of HIV-infected women in Lusaka, Zambia using public sector facilities began ART during pregnancy. The model of care was referral from the antenatal care clinic to a separate ART clinic located on the same site, but physically separate and staffed separately.

In October 2007 the authors introduced a programme providing antiretroviral treatment within the eight busiest Lusaka district public health sector antenatal care (ANC) clinics, called ART in ANC to try and increase use of antiretroviral treatment among HIV-positive pregnant women.

Between October 2007 and May 2008 the programme was rolled out one clinic at a time (stepped-wedge design).

The eight sites were matched into four pairs based on the number of HIV-positive pregnant women expected at each site. All participating clinics began collecting data at the same time while providing the standard of care (referral to ART clinic). Then one by one each clinic crossed over to the ART in ANC intervention. This design allowed for each clinic to provide patients to both arms of the comparison. Each clinic acted as its own control.

Both the separate ART and ART in ANC clinics used the same schedules, laboratory evaluations, record and quality assurance systems. The same cadres of personnel with identical ART training staffed both.

Of the 37,203 patients who began antenatal care in the eight clinics between 16 July 2007 and 31 July 2008, 15% (5667) began antenatal care 60 days before the intervention began. Given the potential for this group to be identified as treatment-eligible in the control period and then start ART in the intervention period they were excluded from the analysis to avoid any potential ambiguity.

37% (13,917) were identified as the referral to ART services (control) cohort (the existing standard of care), as antenatal care began more than 60 days before the start of the intervention. 47% (17,619) started antenatal care 60 days after the intervention began and were classified as the integrated ART in ANC (intervention) cohort.

The study was successful in its aim of finding ways to increase the provision of antiretroviral treatment to eligible pregnant women succeeded.

ART integration into antenatal care clinics more than doubled the percentage of HIV-positive pregnant women starting antiretroviral treatment. The average time women were on ART prior to delivery was at least ten weeks in both cohorts. Studies have shown that using ART for longer than seven weeks before delivery is more likely to result in suppression of viral load and provides a less than one percent risk of perinatal transmission.

The authors note the strengths of the study 1) a large cohort of women in antenatal care were assessed for ART eligibility in eight

busy public sector PMTCT programme sites 2) an integrated electronic patient record system captured comprehensive patient information from ART eligibility, enrollment, starting ART and retention. 3) The phased rollout allows for a controlled evaluation unbiased by time trends and means that all sites are able to benefit from the improved strategy.

A potential weakness, the authors note, is the failure to directly report incidence of infant HIV infection or HIV-free survival. However, they argue that the primary challenge in prevention of mother-to-child transmission (PMTCT) is not whether ART is safe or effective in the prevention of infant HIV infection. Studies have already ably demonstrated this. The main issue, they argue, is increasing coverage of eligible women.

The 90-day retention rate in both cohorts was approximately 90%, and the authors made a programmatic decision to keep women in the integrated clinic until weaning at approximately six months after delivery.

The authors suggest possible reasons why this integrated approach is more effective than the previous standard of care model (referral from ANC to a separate ART clinic):

- Pregnant women may want to avoid enrolling in over crowded ART clinics and not deal with having to go to two separate clinics for care
- Poor staff attitudes in ART clinics toward pregnant women may be a factor; when ART is integrated into ANC staff are more likely to take ownership and initiative in counselling and follow-up of eligible patients
- An integrated clinic provides focus and interest in the provision of ART to eligible women.

While coverage more than doubled, over 60% of those in need are still not accessing treatment. The authors propose that further studies are needed to discover why, and "target strategies to improve uptake further".

The authors conclude that "the cost and human resources involved in implementation of these strategies are areas for future analysis; however, in our setting, we have committed to deploying this strategy to other district clinics, believing it to be an essential step along the pathway to our ultimate goal of eradicating paediatric HIV and promoting maternal health."

Reference

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Antiretroviral therapy

Four million now receiving ART, 5 million still in need

By Carole Leach-Lemens

Although four million people are now receiving antiretroviral treatment in low and middle-income countries, another five million adults and children lack access to treatment, according to figures released today by United Nations agencies.

The report [Towards universal access: scaling up priority HIV/AIDS interventions in the health sector](#) is published by the World Health Organization, UNAIDS and UNICEF, and is the third

annual review of international progress towards the goal of universal access to treatment and prevention by 2010.

Although more than a million people are estimated to have been enrolled into treatment programmes during 2008 alone, the biggest annual increase since treatment scale-up began, only 42% of those in need of treatment in low and middle-income countries are currently being reached.

The report also reveals major gaps in two priority areas, the prevention of mother to child transmission and treatment of children.

The report estimates that 21% of pregnant women received an HIV test in 2008, and 45% received drugs to prevent mother to child transmission, of whom around one-third received only single-dose nevirapine, the least effective form of preventive treatment. Only one-third of those who tested positive were assessed for eligibility for antiretroviral treatment for their own health.

Although 38% of children with HIV in low- and middle-income countries in need of treatment received it, infant diagnosis continues to lag behind. In 41 reporting low- and middle-income countries only 15% of children born to HIV-infected mothers were tested for HIV within the first two months of life.

Background to universal access

In 2001 the convening of The United Nations Special Session on HIV/AIDS marked an historic beginning. For the first time a global set of targets was agreed in response to the crisis. In 2006 at the second United Nations General Assembly High Level Meeting on HIV/AIDS, countries agreed to work towards the goal of "universal access to comprehensive prevention programmes, treatment, care and support" by 2010. The G8 Final declaration in L'Aquila, Italy in July 2009 claimed "We will implement further efforts towards universal access to HIV/AIDS prevention, treatment, care and support by 2010"

WHO, UNICEF and UNAIDS in collaboration with other international monitoring and reporting mechanisms have been monitoring progress, nationally, regionally and globally, of the health sector's response to HIV. The report presented today is the third in a series of annual progress reports towards universal access that includes HIV services for women and children.

WHO together with UNICEF developed a joint reporting tool to request information from national programmes to collect data on the scale-up of health sector interventions in response to HIV. The goal of this process is to facilitate the collection of a standardised set of information.

Indicators in the reporting tool are based on the WHO Framework for Monitoring and Reporting on the Health Sector Response to HIV/AIDS towards Universal Access, and The Report Card on the Prevention of Mother-To-Child Transmission (PMTCT) and Paediatric HIV Care and Treatment coordinated by UNICEF and WHO on behalf of the Expanded Interagency Task Team (IATT) on the Prevention of HIV Infection in Pregnant Women, Mothers and their Children.

Data collected include the number of people on antiretroviral treatment at the end of 2008, disaggregated by age and sex. Validation of data included national authorities, key implementing partners as well as UN and donor agencies at the national, regional and global levels. Following receipt of information from countries on March 31, 2009, validation of data ready for analysis was finalised by April 15, 2009.

139 (out of 149) low- and middle-income countries and 19 high-income countries reported data (among a total of 192 United Nations member states).

By the end of 2008 between 3.7 and 4.3 million people were on antiretroviral treatment including an estimated 275,700 children (38% of those in need) under the age of 15 years.

Progress varies by country and region. In sub-Saharan Africa, for example, where two-thirds of all global infections occur, an estimated 2.9 million people were on treatment by the end of 2008, with an approximate increase of 800,000 people during 2008.

In Latin America, and East, South and South-East Asia antiretroviral coverage is estimated to be 54% and 37%, respectively, whereas in North Africa and the Middle East, and among low- and middle-income countries in Europe and Central Asia, coverage is estimated to be 14 % and 23% respectively.

In 2008 just one percent of pregnant women living with HIV in North Africa and the Middle East received antiretroviral therapy for prevention of mother-to-child transmission.

While there is evidence of increased political commitment for HIV testing and counselling policies, with 90% of reporting countries having national policies in place, knowledge of status remains low; a median of less than 40% of people living with HIV are aware of their status.

The report highlights new data as well as acknowledgment of the dynamics of the epidemic among men who have sex with men, in particular in sub-Saharan Africa where same-sex relations are often considered taboo.

The authors note that population groups at high risk, for example, injecting drug users, sex workers and men who have sex with men, continue to face technical, legal and socio-cultural barriers in accessing health care.

Factors that have hampered progress include weak health care systems, a shortage of health care personnel, stigma and discrimination, and limited access to HIV testing and counselling which is poorly integrated into a continuum of care.

The current global economic crisis not only highlights the obstacles to attaining universal access but also threatens to reverse progress made. Programme budgets will be cut or eliminated and this would mean increasing morbidity and mortality, increasing transmission risks, increased antiretroviral resistance leading to increased burden on health systems and a reversal of economic and social gains.

According to the authors opportunities do exist within this climate. For example, they point to the high levels of commitment pledged to attaining universal access; the increase in access to testing and counselling as well as the emerging evidence on the effects of antiretroviral treatment for prevention of HIV, and they stress that "The hard-won gains of recent years are fragile and call for renewed commitment by all stakeholders."

Reference

WHO, UNICEF, UNAIDS. [Towards universal access: scaling up priority HIV/AIDS interventions in the health sector](#). September 2009.

International donors must not retreat from commitment to HIV treatment scale-up, MSF warns

By Keith Alcorn

A retreat from international funding commitments for AIDS threatens to undermine the dramatic gains made in reducing AIDS-related illness and death in recent years, according to a new report by Médecins Sans Frontières (MSF).

The report highlights a number of signs that donor commitment towards the scale-up of antiretroviral therapy is faltering.

Although many countries have been successful in scaling up treatment services to provide antiretroviral treatment to people in need, few countries have yet achieved the target of universal

access` - diagnosis and treatment of at least 80% of people with HIV with an immediate need for treatment.

According to a [recently published report from WHO, UNAIDS and UNICEF](#), only 42% of people in need of treatment in low and middle-income countries are currently getting it. Nearly five million people are currently in need of treatment.

Loss of momentum in scale-up will lead to continuing high levels of death and illness, and even the erosion of recent gains deaths averted and TB cases prevented, MSF argues.

Major donors are facing significant problems in expanding their commitment, due in part to the economic crisis, but also due to reluctance to devote further resources to HIV treatment at the expense of other health problems.

In the case of the Global Fund to Fight AIDS, Tuberculosis and Malaria, MSF notes that while in 2008 the Fund's board encouraged ambitious country proposals for scale-up, resulting in a 2.5-fold increase in grants, 2009 grants have fallen by 35% compared to 2008 due to a shortfall in donor support for the Fund.

The Fund announced in March 2009 that it faced a \$4 billion shortfall, due in part to the failure of major industrialized countries such as France, Germany, Japan and Italy to make commitments commensurate with their GDP.

The Fund has also imposed a 10% cut in grants already approved, and is considering whether to abandon the automatic extension of grants to programmes that have performed well.

Next week in Addis Ababa the Global Fund's board will vote on whether or not to suspend all new funding proposals in 2010.

In the United States funding for PEPFAR will be frozen at current levels for the next two years, indicating that no further expansion of treatment numbers will be possible.

Governments such as those of Malawi and Uganda are now searching desperately for funds to treat the growing number of people with HIV who will require treatment in years to come.

But the report also notes the failure of most African governments to meet a 2001 pledge to devote 15% of resources to health – only eight have reached this target.

"After almost a decade of progress in rolling out AIDS treatment we have seen substantial improvements, both for patients and public health. But recent funding cuts mean doctors and nurses are being forced to turn HIV patients away from clinics as if we were back in the 1990s before treatment was available", says Dr Tido von Schoen-Angerer, Director of MSF's Access to Essential Medicines Campaign.

"The Global Fund must not cover up the deficit caused by its funders", says von Schoen-Angerer. "The proposed cancellation of the 2010 funding round and other measures to slow the pace of treatment scale-up are punishing the successes of the past years and preventing countries from saving more lives."

[Download the report here.](#)

Global cost of HIV treatment and prevention could reach \$35 billion by 2031

By Carole Leach-Lemens

Without a serious change in approach AIDS will still be a major pandemic and funding required in resource-poor countries could reach an estimated \$35 billion annually, three times the current level, by 2031—the fiftieth year of the pandemic— according to modelling carried out for the AIDS 2031 project by Robert Hecht and colleagues and published in the November/December edition of *Health Affairs*.

Results from the Cost and Financing Working Group, AIDS 2031, headed by Robert Hecht were presented at a Health Affairs briefing on Capitol Hill 'Meeting HIV/AIDS cost demands: is the global response working?' in Washington, DC on November 10 2009.

Others presenting at the briefing included: Anthony S. Fauci, Tom Walsh, Daniel Wikler, Alan E. Greenberg and Shannon L. Hader.

Results support policy choices focusing on investments in high-impact prevention for most-at-risk groups - sex workers, men who have sex with men, and injecting drug users - efficient treatments, new prevention tools together with significant behaviour-change efforts. These could help cut costs by half as well as help control the pandemic.

Progress over the past twenty-five years has been made yet an estimated thirty-three million people are still living with HIV. There were 2.3 million new infections in 2007.

The AIDS 2031 project was set up to see how things might be done differently with the idea that by 2031 there would be few new infections, nearly all those needing treatment would get it and AIDS orphans would be helped to live normal lives. Working groups were formed to examine HIV/AIDS epidemiology, social drivers, leadership, science and technology, financing and sub-regional topics.

The AIDS 2031 Cost and Financing Working Group's estimation of future AIDS costs followed the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global Resource Needs Estimates with some changes. Estimates first done in 2001 evolved to include 48 interventions in prevention, care, treatment, mitigation, programme support and international support.

Estimates for 2031 used target population costs, unit costs and coverage through 2031 and took into consideration interventions such as pre-exposure prophylaxis, microbicides as well as vaccines.

The group calculated costs for low- and middle-income countries (the twenty countries with the most infections plus Mexico and Brazil for geographic representation) using a simple equation: population in need x coverage x unit cost = resources required.

The model has limitations, the authors note, including not taking account of possible synergies between variables. However, they argue, it is intuitive, easy to understand and use.

The authors developed four broad scenarios to look at the financial and epidemiological outcomes of widely varying policy choices and stress that "the four scenarios frame the possibilities and identify actions that could result in better control of the pandemic at lower cost" and include:

- Rapid scale up: Political will is strong, and resource availability continues to grow. It assumes all countries will achieve universal access to key prevention, care and treatment, and support services for vulnerable children by 2015 and continue at that level to 2031. How realistic this is within certain political and capacity contexts is questionable, but it does represent what the authors call a 'what is possible' scenario.
- Current trends: coverage of key interventions continues to grow at recent rates and coverage reaches about two-thirds of universal access targets by 2015 and stays at that level.
- Hard choices for prevention: Limited resources will mean that countries use most cost-effective approaches to achieve maximum impact. Focus is on most-at-risk populations including sex workers, men who have sex with men, and injecting drug users. Countries with low-level and concentrated epidemics will give less attention to general population interventions. Treatment would remain at "rapid scale-up".
- Structural change: Focus is on looking at changes that would reduce vulnerability and help promote a sustained response and include: reducing violence against women, change employment

practices that separate workers from their families, remove legal and stigma-related barriers and strengthen health systems. Such changes will bring better coverage for most-at-risk populations, improved effectiveness of prevention programmes but would take an additional ten years to put in place.

In all scenarios even in the best of circumstances and with the scaling-up of current interventions to the maximum, the authors conclude that new adult infections would only be cut by 48 percent and more than one million would still become infected in 2031.

The authors note that regardless of the "scale-up" strategy, adopted costs will increase rapidly over the next five to eight years and continue to rise over the following 15 years in low- and middle-income countries. All stakeholders, from government, foundations, nongovernmental organisations, households to companies will be under pressure to meet the costs.

Of the four scenarios "rapid scale-up" is the most expensive requiring \$35 billion in 2031 with a cumulative cost of \$722 billion over the next twenty-two years; "current trends" and "hard choices" will cost \$24 billion and \$19 billion in 2031 respectively, with cumulative costs of \$490 billion and \$397 billion.

The "hard choices" scenario is the most cost-effective, achieving almost the same number of infections averted with an incremental cost-effectiveness ratio of \$1,429 for each HIV infection averted. "Rapid scale-up" averts the most infections but is the least cost-effective (\$7,594). "Current trends" and "structural change" are in the middle with \$6,225 and \$6,803 respectively.

Choices made today by governments, international organisations, foundations and civil society groups, the authors argue, will affect how much there will be to spend for AIDS in the future.

They highlight some important policy considerations.

Putting "hard choices" into practice means investing in high-impact prevention efforts for most-at-risk populations - sex workers, men who have sex with men, and injecting drug users - and dealing with the barriers these groups face, such as stigma and discrimination as well as governments' limited willingness to direct resources their way.

Implementation of this scenario also means looking at all drug-related costs including measures such as patent pooling and adopting low-cost, high-quality delivery approaches such as task-shifting.

While broader structural changes may increase costs in the short-term the long-term benefits may result in averting the largest numbers of new infections, in addition to improvements in women's status and economic productivity.

The authors highlight the need for investments in new HIV prevention tools, such as AIDS vaccines and treatments, as well as significant behaviour-change strategies.

They conclude that mobilising the considerable sums required in resource-poor settings between now and 2031 will be difficult. The challenge is to sustain support from individual donors, foundations, and companies, notably from private sources, as well as appealing to new philanthropists emerging not only in Europe and North America but in China, India, Mexico and the Middle East.

Reference

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d4T dose reduction does not result in poorer treatment outcomes in South African patients

By Keith Alcorn

The use of a reduced dose of d4T (stavudine), as recommended by the World Health Organization, did not reduce the likelihood of viral load suppression after six months in a large cohort of South African patients, researchers from the Aurum Institute of Health Research report in the August 24th edition of *AIDS*.

The use of d4T in first-line treatment has been phased out in the developed world due to toxicity, but in developing countries fixed-dose combinations containing d4T are still widely used due to the drug's low cost compared to tenofovir or abacavir. In South Africa d4T remains a staple component of first-line treatment in the public health system, despite widespread calls for its use to be phased out.

The key toxicities associated with d4T are lipoatrophy (fat loss), hyperlactatemia and lactic acidosis, and peripheral neuropathy.

The drug was originally licensed at a dose of 40mg twice daily in adults weighing more than 60kg.

In 2007 the World Health Organization recommended that developing country treatment programmes should use a 30mg dose of d4T if it was not possible to phase out use of the drug. Their recommendation was based on a number of small studies which showed no negative effect of using a lower dose in adults weighing more than 60kg.

Adoption of the 30mg dose has been slow in some national programmes, and data are still lacking from an African population on the virological effects of initiating therapy with a lower dose of d4T.

Researchers at the Aurum Institute in Johannesburg analysed data from 618 patients enrolled in community-based HIV care programmes in South Africa who initiated treatment containing d4T between January 2006 and January 2008. All patients had been followed for at least six months after starting treatment, and weighed at least 60kg at baseline.

Of the eligible patients, 110 received a 30mg dose and 508 received a 40mg dose. Those receiving a 30mg dose were slightly more likely to receive nevirapine than efavirenz and to have WHO stage 4 HIV disease, and had significantly lower baseline CD4 counts (91 vs 115, $p=0.0001$). These differences were not a result of individualisation of treatment, say the investigators, but due to a change in guidelines during the period under study.

There was no significant difference after six months of treatment in the proportion of patients who had viral load below 400 copies/ml or 50 copies/ml (79% vs 81% and 60% vs 58% respectively). Multivariate analysis which adjusted for NNRTI agent, baseline viral load and weight showed no effect of dose on viral suppression.

The investigators say their findings provide additional evidence to support the WHO recommendation, but note that evaluation of long-term side effects according to dose is essential.

Reference

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Cost-effective ways to reduce loss to follow-up in ART programmes identified

By Keith Alcorn

Measures to reduce loss to follow-up in antiretroviral treatment programmes such as abolishing user fees, paying transportation costs, providing meals and improving staff training would be cost-effective even if they prevented less than half of patients from

failing to return to the clinic, according to projections based on data from Côte d'Ivoire.

The study, published in the October edition of *PLoS Medicine*, was designed to examine the cost-effectiveness of various measures to improve patient retention in care.

Loss to follow-up is a serious problem in treatment programmes in low and middle-income countries. Patients who are lost to follow-up are often sicker, and without regular medical attention and antiretroviral treatment may either die or return to hospital with serious illnesses or drug resistance due to interrupted treatment.

These outcomes result in increased costs for the health system and an increased burden for affected families.

Using data from the Aconda programme, an Abidjan-based organisation providing antiretroviral therapy to around 6,700 patients, researchers from nine institutions in the US, France and Côte d'Ivoire modelled the effects of several different interventions designed to reduce loss to follow-up on life expectancy and cost-effectiveness.

The interventions analysed were chosen with a view to addressing some of the key factors repeatedly associated with loss to follow-up in studies in sub-Saharan Africa: user fees for HIV care; the cost of transport to the clinic; need to obtain food instead of attending the clinic, and lack of staff follow-up of defaulters.

Detailed description of the methodology and results is available [in an open-access paper](#).

Assuming that 18% of patients were lost to follow-up within one year of initiating treatment, and did not return until they developed an opportunistic infection, they found that the life expectancy of patients lost to follow-up during the first year of treatment would be halved. If they never returned to care they would be dead within two and half years.

Based on the GDP per capita of Côte d'Ivoire, strategies to reduce loss to follow-up would be cost-effective if they cost less than \$2832 per year of life saved.

Stopping co-payments for antiretroviral therapy would be cost-effective at a cost of \$22 per person per year if it reduced the rate of loss to follow-up by 12% (i.e. from 18% to 16%).

Using a combination of methods for preventing loss to follow-up would be cost-effective at a cost of \$77 if they reduced loss to follow-up by 40% (i.e. from 18% to 10.8%). In the Aconda programme loss to follow-up was reduced by 40% through a single intervention, phoning or visiting patients who missed clinic appointments. This intervention cost between \$22 and \$53 per patient per year.

The study has a number of limitations, the authors note. It may not be possible to generalise the findings beyond Côte d'Ivoire, or beyond clinics with specialist skills in patient management. The study also lacks firm evidence on the extent to which various interventions reduce loss to follow-up; the researchers were forced to extrapolate from various studies.

Further operational research on easily replicable methods of reducing loss to follow-up is needed, but the findings of the study will strengthen the case for abolishing user fees. Although the [World Health Organization recommended the removal of user fees for HIV care in 2005](#), fees for services such as tests and consultations remain in place in many countries.

However, removing financial barriers is only one aspect of reducing loss to follow-up. Professor Anthony Harries, who has advised the Malawi government on its HIV and TB programmes, [told the 2009 HIV Implementers' conference](#) that reducing loss to follow-up requires a wide range of interventions, including improved record-keeping, reliable drug supplies, decentralisation of care and creative approaches to maintaining adherence.

In a [related Perspective article in *PLoS Medicine*](#), Gregory Bisson of the University of Pennsylvania School of Medicine and Jeffrey Stringer (of the University of Alabama School of Medicine), both uninvolved with the research, agree that improving retention in HIV/AIDS care makes programmatic and economic sense. They stress that "the major AIDS donors, such as the US President's Emergency Plan For AIDS Relief (PEPFAR) and the Global Fund, should be keenly interested in this issue, and willing to invest in strategies to improve retention."

Further information

See [HIV & AIDS Treatment in Practice 90, August 2007](#) for an extended review of strategies to address loss to follow-up, *A follow up on follow up: switching to a community-based response to improve retention in care*.

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Treatment as prevention

High probability that HIV viral load remains suppressed between tests: implications for infectiousness debate

By Michael Carter

Individuals who are taking antiretroviral therapy and have had their viral load suppressed to undetectable levels can be confident that it will remain undetectable between tests, suggest the results of a Swiss study published in the September edition of *HIV Medicine* suggests.

Most increases in viral load were low-level and transient, but a small number of patients experienced a rebound in their viral load to the potentially infectious level of 1000 copies/ml or above without there being any ready explanation. The findings of this research will inform debates about the potential infectiousness (or otherwise) of individuals taking suppressive HIV therapy.

[In January 2008, senior HIV doctors in Switzerland issued a statement that concluded that patients taking antiretroviral therapy who had had their viral load suppressed to undetectable levels of at least six months were extremely unlikely to be infectious for their heterosexual partners.](#)

Considerable controversy surrounded the statement, and one of the objections raised against it was the reliability of an undetectable viral load: could an HIV-positive individual who had an undetectable viral load the last time it was measured be confident that it was still undetectable when they had sexual intercourse?

To test this, investigators from the Swiss HIV Cohort looked at the likelihood of successive viral load tests being undetectable. "By analogy", they write, "this likelihood also applies to sexual contact some time after a measured undetectable viral load, a situation where real-time measurements are not practicable."

The study population involved 6168 patients taking antiretroviral therapy who had at least two successive viral load measurements below 50 copies/ml between May 2003 and the end of 2007.

Just under two-thirds of these patients started antiretroviral therapy with a potent triple-drug combination.

At the time viral load was measured, 80% of patients stated that they had been 100% adherent to their antiretroviral therapy in the previous four weeks. However, the investigators think this is likely to be an over-estimate given the social-desirability of reporting good adherence to the study interviewers.

Viral load rebounded to above 50 copies/ml on at least one occasion in 43% of patients, and above 1000 copies/ml – the level at which transmissions have been recorded – in 7% of patients. The median interval between viral load measurements was 93 days.

If more than one dose of HIV treatment was missed between viral load measurements, the probability of it remaining undetectable between tests was 70%. If one dose was missed the probability increased to 85% and if no doses were missed to 86%.

Viral load was more likely to remain suppressed in successive tests in individuals who started HIV therapy with a triple-drug combination, with the probability of sequential undetectable viral load measurements being 95%.

Factors significantly associated with successive undetectable viral loads included a higher number of previous visits with suppressed HIV, type of antiretroviral therapy, being on initial HIV treatment combination, and interval between tests (all $p < 0.001$).

Most increases in viral load were low and transient. In 66% of patients it rebounded to below 200 copies/ml, and in two-thirds of patients whose viral load increased to below 1000 copies/ml it was once again undetectable in the following test. The same was true for 30% of individuals whose viral load increased to over 1000 copies/ml.

Overall, there was a 98% probability that viral load would not rebound from undetectable to the potentially infectious level of 1000 copies/ml or above in successive tests. If an individual had started HIV treatment with a triple combination of drugs this increased to 99%.

The investigators examined rebounds in viral load to 1000 copies/ml or more in greater detail. In 78% of cases there was an explanation for this, for example poor adherence. However, “for the remaining 22%, no plausible explanation could be found.”

Adherence and the potency of HIV treatment were the two key factors associated with suppression of viral load in successive viral load tests, stress the investigators. They note that both of these issues were noted as factors affecting viral load suppression in the Swiss Statement on infectiousness.

Although the results of the study showed a high degree of probability that viral load remained suppressed in individuals between tests, the “data leave open the possibility that unexplained rises in viral load above 1,000 copies/ml, although rare, may occur.”

Reference

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Flares of genital ulcer disease common in women starting HIV treatment, could temporarily increase infectiousness

By Michael Carter

Genital ulcers frequently flare-up in women starting HIV treatment, a Kenyan study published in the online edition of the *Journal of Acquired Immune Deficiency Syndromes* suggests. A low CD4 cell count when HIV treatment was started and a history of genital ulcers were risk factors for these short-term episodes of genital disease.

“Because genital ulcerative disease flares during the early period after antiretroviral therapy initiation could increase HIV infectivity, pre-treatment counselling include information about ways to reduce the risk of HIV transmission to sexual partners”, comment the investigators.

Genital ulcers are common in women with HIV. Sexually transmitted infections, especially herpes simplex virus-2 are frequently the cause. As such ulcers can cause both damage to the mucus membrane and inflammation, they may increase HIV viral load in the genital compartment, therefore meaning that there could be a greater risk of HIV transmission to sexual partners.

Soon after starting HIV treatment, some patients experience immune reconstitution illnesses. These can involve a temporary worsening of pre-existing conditions, including genital ulcer disease.

To obtain a better understanding of the frequency and timing of genital ulcer disease in women starting HIV treatment, investigators designed a prospective study involving 134 women starting HIV treatment for the first time. The study lasted six months. At baseline and regular intervals after initiating antiretroviral therapy, the women were questioned about the presence of genital ulcers and had a physical examination.

The median CD4 cell count when HIV treatment was started was 127 cells/mm³, and 82 women (62%) reported a history of genital ulcers at some point before starting HIV treatment.

After starting HIV treatment, genital ulcers were reported or observed in 54 women (40%) at 85 study visits (10%). The ulcers were detected by patient report only in 47% of cases, by physical examination in 38% of cases, and by both in 18%.

At baseline, the prevalence of genital ulcer disease was 10%. This increased to 17% after one month of HIV treatment, but fell to 6% after six months of antiretroviral therapy.

In the first set of statistical analysis, a baseline CD4 cell count below 100 cells/mm³, an AIDS diagnosis, and a history of genital ulcers were all significantly associated with a flare-up of genital ulcers during follow-up.

Subsequent analysis that controlled for potentially confounding factors showed that a history of genital ulcers remained highly significant (odds ratio [OR], 3.8; 95% CI: 1.9-7.7, $p < 0.001$), but a low baseline CD4 cell count was of only borderline significance (OR, 1.8; 95% CI: 1.0-3.4, $p = 0.06$).

Next the investigators restricted their analysis to cases of ulcerative disease which were diagnosed by physical examination. One month after starting HIV treatment, there was a 40% increase in the prevalence of genital ulcers from baseline in this subset of women, but this had fallen to 20% by month two, and after three months of HIV treatment, was below baseline levels. Both a baseline CD4 cell count below 100 cells/mm³ and a previous history of genital ulcers were highly significant predictors (both $P < 0.001$) of flares in genital ulcer disease after starting anti-HIV drugs.

“We found that genital ulcer disease prevalence was relatively high at baseline (almost 10%), increased almost 2-fold in the first month, then returned to baseline thereafter”, write the investigators.

They therefore conclude, “although all women initiating antiretroviral therapy should be counselled about strategies for reducing their risk of transmitting HIV to sex partners, the data presented here suggest that women with a history of genital ulcer disease may benefit from additional risk reduction counselling regarding the potential for increased transmission risk in the first 1-2 months of therapy.”

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How much does viral load need to fall to halve HIV transmission risk?

By Keith Alcorn

An average viral load reduction of 0.74 log is needed in order to reduce the risk of HIV transmission by 50%, according to an analysis of the Partners in Prevention study of aciclovir as an HIV prevention measure. The finding was presented at the AIDS Vaccine 2009 conference, but also has important implications for future studies of HIV treatment as prevention.

The link between plasma viral load – the level of HIV in the blood – and sexual transmission of HIV is [well established, and a number of studies have sought to establish the risk of HIV transmission at different levels of viral load.](#)

However, until now there has been little information about the extent to which varying degrees of viral load reduction might correlate with reductions in the risk of HIV transmission.

This information could be important in designing studies of the impact of interventions such as antiretroviral treatment on new infections, or of vaccines that affect the post-infection viral load even if they do not prevent infection (so-called sterilising vaccines).

Dr. Jairam Lingappa of the University of Washington, Seattle, and colleagues from the Partners in Prevention study of aciclovir treatment in HIV-positive people with HSV-2 coinfection, presented an analysis of viral load in the partners of individuals who became infected during the study.

The Partners study, [previously described in detail here](#), recruited 3408 individuals and monitored HIV-serodiscordant couples every three months to detect new HIV infections and to measure viral load in the HIV-positive partner.

If HIV infection was detected in previously seronegative partners, viral sequencing in both partners was carried out in order to determine whether the primary partner was the source of infection.

This analysis revealed 108 linked infections, with viral load measurements available from the transmitting partner within the preceding three months.

(An obvious limitation of this method is that it cannot account for temporary viral load increases due to infections such as malaria that would not be fully captured by the three-month window between measurements, or sexually transmitted infections that would not affect plasma viral load but which would nevertheless increase genital viral load).

In this study individuals with HIV and HSV-2 were randomised to receive aciclovir treatment or placebo, to test whether aciclovir prophylaxis reduced the risk of HIV transmission.

Although the researchers noted a median viral load reduction of -0.25 log in those who received aciclovir, this specific analysis was not looking at the effects on HIV transmission of any HIV viral load reduction as a consequence of aciclovir prophylaxis.

The researchers stratified individuals according to their viral load over time, and then calculated the HIV incidence per 100 person-years for each viral load stratum.

Viral load stratum	2 - 3log (<1000 copies)	3 - 4log (<10,000 copies)	4 - 5log (<100,000 copies)	5 - 6log (<1 million copies)	6 - 7log (<10 million copies)
Transmission events	3	10	58	38	3

Person-years of follow-up	954	1382	1772	805	53
Incidence per 100 PYS	0.3%	0.7%	2.9%	4.7%	5.7%

The vast majority of follow-up and transmission events occurred in the viral load range between 3 and 6 log (1000 to 1 million copies/ml), with evidence of substantial reductions in the risk of transmission between each stratum as viral load fell lower.

Combining data from all strata, the researchers calculated that regardless of the baseline viral load, an average viral load reduction of 0.74 log would result in a 50% reduction in the risk of HIV transmission across the whole cohort. Extrapolating from the data presented, this degree of reduction would clearly have the greatest prevention impact in people with higher levels of viral load, since this is where over 90% of transmission events occurred.

Jairam Lingappa noted that the 2.1% HIV incidence observed in this study population was vastly lower than the HIV incidence observed in recent population cohort studies in Uganda and Zambia, and was likely to be attributable to the intensive counselling and condom provision for study participants.

Thus, a reduction of 0.74 log might result in a much larger number of infections averted at higher levels of HIV incidence, even if the reduction in risk of transmission remained consistent at 50%.

However, that hypothesis would need to be tested in a population study. This study looked at viral load and transmission only in serodiscordant couples where transmission could be proved, in which the majority of sexual contacts were within couples throughout the study, and where intensive counselling took place, rather than in a population where much wider sexual mixing may occur.

A forthcoming meeting organised by the World Health Organization will review the research questions that need to be addressed in order to establish the prevention effects of viral load reductions due to antiretroviral treatment.

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Tuberculosis

TB treatment guidelines need to change, systematic reviews show

By Keith Alcorn

International guidelines for treating tuberculosis need to be updated to recommend six months of rifampicin treatment in first-line therapy for all countries, and to improve the ways in which relapsers and isoniazid-resistant patients are treated, according to two systematic reviews published this week in the open access journal *PLoS Medicine*.

Public health programmes in many countries follow guidelines developed by the World Health Organization guidelines for treatment of tuberculosis (TB). However, these guidelines have not been revised since 2003 and are due to be updated in 2009.

Dr Dick Menzies, director of the Respiratory Division of McGill University, Montreal, and colleagues from the United States and the International Union Against Tuberculosis and Lung Disease carried

out two systematic reviews of the scientific literature to assess the evidence on several controversies in TB treatment:

- How long should patients receive rifampicin in first-line treatment? The current recommendation is for two months of rifampicin, isoniazid, ethambutol and pyrazinamide, followed by 4-6 months of continuation treatment with two antibiotics. Although many countries use rifampicin in the continuation phase, the practice is far from universal. Are rates of failure, relapse and drug resistance higher with a shorter duration of rifampicin treatment?
- How should patients who fail to respond to first-line treatment be treated, especially those without resistance or with resistance only to isoniazid? The current recommendation is that these patients should receive an 8-month course of isoniazid, rifampicin and ethambutol, with pyrazinamide and streptomycin added for the first three and two months respectively.

The studies were partially funded by the World Health Organization in order to inform the development of new TB treatment guidelines.

Rifampicin in first-line treatment

In the first study, the researchers identified and analysed 57 randomised, controlled clinical trials including more than 20,000 participants treated for TB conducted since 1965.

They found that regimens using the drug rifampicin for only the first two months had significantly higher rates of failure, relapse, and acquired drug resistance compared with regimens that used rifampicin for at least six months.

Based on the pooled risk differences from the trial analyses, the reviewers estimate that treatment of 100 patients with a two-month rifampicin-containing introductory regimen, followed by isoniazid/ethambutol for six months (still standard practice in at least 24 countries, according to WHO), would result in 13 more treatment failures or relapses per 100 patients treated when compared to six months of rifampicin-containing treatment.

Patients who had drug resistance at baseline were at particularly high risk of poor treatment outcomes if they received only two months of rifampicin treatment.

The investigators note that because most studies pre-dated the AIDS epidemic it is not possible to provide definitive information about the duration of rifampicin treatment in HIV/TB-coinfected people.

They say that more research is needed in the form of adequately powered clinical trials to determine optimum dosing schedules, management of isoniazid monoresistance and the optimal duration of treatment to prevent relapse.

Some countries have implemented three-times-a-week dosing of rifampicin during the introductory phase of treatment in order to improve the ability of health systems to provide directly observed therapy. The reviewers found that this intermittent dosing schedule was associated with an increased risk of acquired drug resistance, but not of relapse or treatment failure.

Relapsers, non-responders and isoniazid-resistant patients

The second study analysed trials of TB treatment in previously treated individuals who had relapsed after treatment or failed to respond to treatment, or those with isoniazid-resistant infection. (It is important to note that this does not include the more-difficult-to-treat patients with multidrug resistant TB).

The authors note that 10-20% of patients receiving TB treatment in low and middle-income countries require re-treatment, and say that the re-treatment regimen plays a key role in any DOTS strategy.

The researchers found no randomised trials comparing the currently recommended WHO retreatment regimen against other approaches. In non-comparative (cohort) studies, failure rates were

generally low if participants were infected with strains that were sensitive to all antibiotics in the regimen.

However, in studies in which participants were infected with a strain of *Mycobacterium tuberculosis* resistant to one or more drugs, failure rates ranged from 9% to 45%.

The researchers also analysed the combined results of 33 trials that investigated the effect of various regimens on almost 2,000 patients (some receiving their first treatment for TB, others being retreated) with resistance to isoniazid alone.

This meta-analysis found lower relapse, failure and acquired drug resistance rates to be associated with longer duration of rifampicin treatment, daily therapy early in treatment, inclusion of the drug streptomycin, and regimens that included a greater number of drugs to which the patient's TB infection was sensitive.

Nevertheless, the authors say that "the current body of evidence for treatment of previously treated patients is a dog's breakfast...The current re-treatment regimen was not tested and refined in a sequence of randomized trials. Instead, this regimen was the product of expert opinion."

The most immediate needs identified by the review, they say, are increased access to drug sensitivity testing, and a redesigned re-treatment regimen that is based on the assumption that in the future all patients will have received a six-month course of rifampicin.

Studies of re-treatment regimens need to be given greater priority, they point out, because cases of monoresistance in TB patients remain around five times more common than multidrug resistance (MDR), and because of the extreme weakness of the evidence base regarding retreatment of isoniazid-resistant TB patients. "An effective regimen for the group that requires re-treatment could reduce generation of MDR," they conclude.

Taken together, these findings will inform upcoming revisions of the WHO TB treatment guidelines, and identify an important need for clinical trials to evaluate dosing schedules, detection and management of isoniazid resistance, and the optimal duration of treatment to prevent relapse, as well as more effective approaches to retreatment of tuberculosis. International, multicentre trials recruiting large numbers of patients will be needed.

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Vaccines

Vaccine reduces risk of HIV infection by one-third in large trial

By Keith Alcorn

A combination of two HIV vaccines reduced the risk of infection by almost one-third in a large trial in Thailand, the trial sponsor announced today. It is the first proof that a vaccine against HIV can protect against infection, but scientists say a lot more research will

be needed before a vaccine emerges that can be given to large numbers of people.

"This is a historic day in the 26-year quest to develop an AIDS vaccine," said Dr Alan Bernstein, executive director of the Global HIV Vaccine Enterprise.

"This is the first HIV vaccine candidate to successfully reduce the risk of HIV infection in humans. We are very excited and pleased with the outcome of this trial and congratulate all those who participated in it," said Lieutenant General Eric Schoomaker, Surgeon General, US Army, the trial sponsor.

The trial, called RV 144, compared a regimen of vaccination with two products against vaccinations with a dummy, inactive substance in 16,000 adults enrolled since 2003.

The study recruited adults in the community in two provinces of Thailand with high HIV prevalence (Chon Buri and Rayong), but did not specifically target individuals at high risk of HIV infection. Volunteers for the study were adults aged 18-30 who gave informed consent to participate in the trial.

Participants were randomly assigned to receive an initial set of vaccinations with ALVAC, and follow-up booster vaccinations with AIDSVAX, a product previously tested in large trials without evidence of success, or the placebo vaccination.

The presence of AIDSVAX in the vaccination regimen was one reason why many vaccine experts had not expected the trial to show a positive result.

In the event, the prime-boost combination of ALVAC(R) HIV and AIDSVAX(R) B/E lowered the rate of HIV infection by 31.2% compared with placebo. This reduction was statistically significant, meaning that the possibility that the possibility of the result being due to chance is very low, but the confidence intervals for the estimate in the reduction in risk were wide ($p=0.039$, 95% confidence interval 1.1% - 51.1%).

In the final analysis, 74 placebo recipients became infected with HIV compared to 51 in the vaccine regimen arm. The vaccine regimen had no effect on the amount of virus in the blood of volunteers who became HIV-infected during the study.

More detailed results of this study will be presented next month at the AIDS Vaccine Conference, October 19 - 22 in Paris, France.

The vaccine products used in the study will not go forward for immediate licensing. Instead, the results from the study, which was considered to be a 'proof of concept' trial, will be used to inform the design of future vaccine trials.

Collaborating partners on this study include the US Army, the Thai Ministry of Public Health, the United States National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, sanofi pasteur (the developer of ALVAC), and Global Solutions for Infectious Diseases (GSID), the current developer of AIDSVAX. The collaborators are already working with external experts to determine the need for additional studies on this vaccine regimen and consider the impact of this study's findings on other HIV vaccine candidates.

An unpopular vaccine study produces surprising result

By Keith Alcorn

[The positive results of the Thai HIV vaccine study announced today](#) are surprising to many, since it was widely predicted that the study would fail to show a protective effect.

About the study

The vaccine regimen was designed to stimulate both the cellular and the antibody-producing arms of the immune system (for further

information about vaccines and how they work, [see our guide to HIV vaccines](#)).

First, participants would receive ALVAC, a vaccine that used a canarypox vector to deliver selected recombinant HIV sequences in order to stimulate the cellular arm of the immune system to produce HIV-specific cytotoxic T-lymphocytes (CD8+ cells).

Participants received four doses of ALVAC over six months, and vaccinations at months 3 and 6 with AIDSVAX B/E, a vaccine designed to produce an antibody response against the gp120 protein on HIV's surface, using sequences from two HIV subtypes present in Thailand, B and E.

All participants received counselling on how to protect themselves against infection at the beginning of the study and every six months, as well as being tested for HIV every six months. Anyone who seroconverted during the study received free care and treatment for HIV infection.

The study recruited 16,402 volunteers aged 18-30 in Thailand. All participants were followed for at least three and a half years.

An unpopular study

The RV-144 trial was the biggest HIV vaccine study conducted to date, dwarfing all the other efficacy studies that have taken place, and one that many advocates and scientists said should never have gone ahead.

Back in 2004, as the first participants began to receive vaccinations in Thailand, a group of some of the biggest names in US vaccine research published a letter in *Science* magazine in which they called for the study to be abandoned.

In particular, researchers were concerned that the products being tested in the vaccination regimen, ALVAC and AIDSVAX, had little chance of producing robust immune responses that would protect against HIV infection, based on the results of previous studies.

They expressed concern over the use of AIDSVAX, after phase III trials in the United States and Thailand reporting in 2003 had shown the vaccine to be "completely incapable of preventing or ameliorating HIV-1 infection."

The trial was going ahead, at a cost of over \$119 million over six years, they said, without a clear scientific rationale. They feared that failure of the study would erode the confidence of public and politicians in HIV vaccine research. Plans for a similar study in the US had been cancelled following the results of the AIDSVAX studies.

Instead, they argued, money should be invested in vaccine prospects that showed evidence of strong immunologic responses in phase I and II studies. (For further information on the debate over the Thai trial, see [Types of HIV vaccines](#)).

The RV 144 study continued, despite the controversy, but with little expectation in the wider HIV vaccine field that it would yield a positive result showing a protective effect.

Instead, there was growing optimism that a new vaccine candidate that elicited promising immune responses, developed by Merck, would prove successful in proof of concept studies taking place in the US, Latin America and South Africa.

It was thus a huge shock to the field, when almost exactly two years ago, the investigators in the major study of the Merck vaccine decided to halt [the STEP trial](#) following evidence that the vaccine was not effective.

Worse was to follow, as [subsequent analysis showed](#) that a subset of participants who received the vaccine were at higher risk of infection. The mechanisms that placed these individuals at higher risk are still not understood.

So, today's announcement that the 'Thai trial' resulted in a reduced risk of infection for those who got the vaccine is one of the

bigger surprises in a field that is becoming accustomed to results that upset the conventional wisdom.

However the design of the Thai trial still leaves a major question unanswered. What part of the vaccine regimen induced protection? Was it ALVAC, which had never been tested in an efficacy trial in HIV-negative individuals? Was it AIDSVAX, despite its failure to protect in two large trials in the US and Thailand? Or was it the combination of the two, despite no clear scientific rationale for why the two vaccines together would be expected to produce a greater protective effect than ALVAC alone?

Some of these questions may be answered when further results from the study are presented at the 2009 AIDS Vaccine Conference next month in Paris, but others will require further clinical studies before the mechanisms that led to a modest level of protection in the Thai study are fully understood.

More information and analysis

See also [Vaccine reduces risk of HIV infection by one-third in large trial](#).

See also [Vaccine trial "is the beginning" of a new path of research, says US health chief](#).

Further information

See [aidsmap.com's](#) guide to [The search for an HIV vaccine](#) for further background information.

Vaccine trial "is the beginning" of a new path of research, says US health chief

By Gus Cairns

General Eric Schumaker, Surgeon-General of the US Army, said today that the result of the RV144 HIV vaccine trial - [see this report](#) - "opened new doors and switched on lights" in the field of HIV vaccine research but emphasised that the "modest" efficacy seen in the trial posed more new questions than it provided answers.

Dr Anthony Fauci, the Director of the US National Institute of Allergies and Infectious Diseases (NIAID), said: "This is the beginning of a new HIV vaccine research effort, not the end."

But he added: "This is a welcome and exciting result in a field characterised by disappointment in the last two decades."

The trial today produced an unexpectedly positive result when 31% fewer infections were seen in recipients of the combined ALVAC/AIDSVAX prime-boost vaccine than in placebo recipients, despite previous trials of both individual vaccine concepts producing negative results.

"This trial poses fundamental 'black box' questions," Fauci continued. "What are the correlates of HIV immunity? Has this trial overturned our understanding of what might constitute a protective response to HIV? Can we improve on this efficacy? And does this result mean we should refocus more on clinical research than basic science?"

He answered his own last question by saying "Not at all. NIAID's commitment to keeping an appropriate balance between basic science and vaccinology versus empirical clinical trials has not changed."

Fauci was referring to the controversy which has dogged the RV144 trial - [see this report](#) - which included a group of scientists condemning the trial as a waste of money (NIAID funded three-quarters of the trial's \$105 million cost). But those who said the trial should go ahead, and that the discovery of vaccines has relied as much on serendipity as scientific rationale, appeared today to be vindicated.

The Principal Investigator of the Thai trial, Dr Supachai Jerks-Ngam, said: "We did hesitate to continue the trial because of

the criticism from the scientific point of view. But in view of the need for an HIV vaccine, and in consultation with many international experts, we decided to move forward. That determination turned out to be very significant."

Colonel Nelson Michael, Director of the US Military HIV Research Programme (MHRP), which funded the other 25% of the trial, said that the most surprising and probably significant aspect of the result was that the vaccine appeared to produce a mild protective effect while producing no effect on the viral load in those who were infected.

"We are humbled by this finding," he said. "This may have turned several key assumptions in HIV vaccine research on their heads." He added that the trial showed that "human experimentation trumps everything we do in animals and test tubes."

What Michael was referring to is that the RV144 trial consisted of two vaccines with two modes of action. The 'prime' vaccine, ALVAC, consisted of HIV genes contained in a canarypox virus vector. This model of vaccine delivery was designed to stimulate a cellular immune response. This does not prevent initial infection, but the scientific model - supported by data from some monkey studies - was that the cytotoxic T-lymphocytes (CTLs or CD8 cells) thereby generated would subsequently reduce HIV proliferation, contain viral load, and slow or stop progression to AIDS.

ALVAC appears to have made no difference to viral load at all, a finding at least in harmony with the failure of the [STEP Trial](#) of a CD8 vaccine in 2007; but at the start of RV144 study, CTL vaccines appeared promising.

AIDSVAX, on the other hand, was designed to produce an antibody response against the gp120 protein on HIV's surface, a concept thought to have been discredited in 2003, just after RV144 started, when it failed [an earlier trial](#). The assumption was that HIV's genetic hypervariability would mean that any antibody response would be hopelessly specific; at the time HIV research pioneer Dr Robert Gallo said: "This is not a vaccine approach that was based on science."

Nonetheless what RV144 appears to have done is block infection without containing viral load in those infected, which looks like an antibody response, though Nelson Michael added that a longer-term study, RV152, was following up a proportion of trial participants to see if there were longer-term effects on viral load.

When asked what was causing the vaccine's efficacy, Anthony Fauci commented: "Simply, we don't know. We did not see broadly neutralising antibody responses, though there is an indication of a small antibody response. We also saw a lympho-proliferative response but didn't see an increase in CTLs."

"We may not even have started to measure the correct immune parameters in the body that in fact indicate protection against HIV."

Fauci said there were a number of further questions left unanswered by the trial. These included:

- Was the vaccine's effect durable or would further boosters be needed?
- Are there ways of improving this model's efficacy?
- Would we see similar results in high-risk populations such as men who have sex with men, injecting drug users, and high-risk heterosexuals?

Regarding the last question, MHRP Deputy Director Jerome Kim said that contrary to some reports RV144 did not exclude high-risk people. At baseline a small number of participants did turn out to be MSM and sex workers. The trial was designed to vaccinate a "community sample", in other words a truly representative cross-section of the Thai population, "ranging from people at high risk to people at no risk".

However, Kim also speculated, one reason for the positive result may have been that “the average intensity of exposure to HIV may have been lower than in high-risk populations...we know a sufficiently large inoculum of virus can overcome any vaccine-generated response.”

When asked what scientific studies of the RV144 protocol would come next, given this positive result, Don Francis, Director of Global Solutions for Infectious Diseases and the man who developed AIDSVAX, indicated that there were only enough stocks of remaining vaccine to conduct very small trials – possibly an indication of the unexpectedness of the result. Anthony Fauci said that the first step was to convene a collaborative meeting with outside experts to understand how the vaccine works.

In response to a press question about whether the trial would lead to licensing the current vaccine protocol, Francis and Sanjay Gurnathan of Sanofi Pasteur, who developed ALVAC, emphasised that the study was not powered for approval by the US Food and Drug Administration and that although the threshold of efficacy above which a vaccine might be deemed to be worth using was up to individual countries, the efficacy seen was only modest. “What is on the cards is a series of investigations over the next few years to extend the findings,” commented Gurnathan.

Nelson Michael added that the power of the trial to detect efficacy was greater while it was being designed than turned out to be the case, because of Thailand’s successful attempts to reduce HIV incidence in the trial population.

Nonetheless, the researchers concluded, the trial results mark a turning point in the history of HIV vaccine development. General Schumaker summed up by saying that this is a “great moment for the world of medicine and for the global human family.”

Thai HIV vaccine study: modest effect is real, argue researchers

By Keith Alcorn

The modest protective effect of the HIV vaccine combination used in the [Thai vaccine trial announced last month](#) is statistically significant and not the result of massaging the statistics to produce a positive result, study investigators said at the AIDS Vaccine 2009 conference in Paris today.

The protective effect of the vaccine had been called into question following the release of headline results from the study in late September, which showed that the vaccine reduced the risk of HIV infection by 31%, a result that was statistically significant.

However, at the time of the announcement [attention was drawn to the very wide confidence interval of this estimate](#). Statisticians estimated that the result lay between 1.1% and 51.6% with 95% confidence; in other words, there was a 5% possibility that the result lay outside these bounds.

Subsequently, news leaked on other data from the trial, which suggested that if analysed in other ways, the results were not statistically significant. In particular, concerns were raised about why the results of the less encouraging per-protocol analysis were not released to the world’s press at the same time as the headline result.

Today Dr Nelson Michael of the US Military HIV Research Program explained the three analyses of the study and why the investigators chose to release one particular analysis last month, ahead of the AIDS Vaccine 2009 conference.

Three analyses of the study were planned:

- An intent-to-treat analysis, which included all trial participants randomised, regardless of whether they received the vaccine or not.
- A modified intent-to-treat analysis, which excluded any randomised participant who was discovered to have evidence of HIV infection through viral load testing prior to vaccination. This analysis includes study participants who may have missed some of the vaccinations, and goes some way to estimating the real-life efficacy of the vaccine.
- A per-protocol analysis which excluded all participants who missed any doses of the vaccine, or who received vaccinations on days other than scheduled study visits. A per-protocol analysis in a vaccine study is designed to test the efficacy of a particular vaccination schedule, and is most useful in a study that is intended to lead to product licensing.

The headline results of the study, released last month, indicated that the vaccine reduced the risk of infection by 31%, but the statistical confidence intervals were very wide (between 1.1% and 51%). Nevertheless the result was statistically significant ($p=0.04$).

Other results were not released to the press in September, said Dr Jerome Kim of the US Military HIV Research Program, because they were already embargoed prior to the AIDS Vaccine 2009 conference. But researchers had to honour their commitment, made at the outset of the study, that the Thai people would be the first to hear the result of the trial, so the modified intent-to-treat analysis was revealed in September.

The strict intent-to-treat analysis, however, showed that the reduction in the risk of infection in the vaccine group was not statistically significant (-26.4%, 95% confidence interval -4% to 47.9% ($p=0.08$)). This analysis included seven participants who turned out to have been infected at the time of randomisation, prior to the first shot of vaccine. These infections were identified when stored samples taken at baseline were tested after the participants tested positive at the time of their fourth vaccination.

Similarly, the per-protocol analysis, which excluded around 25% of study participants and thus failed to capture around 31% of infections that occurred during the study (just over half of them in the first six months), showed a reduction in risk of 26.2% (95% confidence interval -13.3% to 51.9%, $p=0.16$).

The full results were also released online today by the *New England Journal of Medicine* and, in their report, the investigators note that the result of the modified intent-to-treat analysis remained statistically significant regardless of the statistical method used to test significance. The investigators used no fewer than six different tests to query the magnitude and robustness of the effect observed, and found that all produced results within the same range, a p value lying somewhere between 0.03 and 0.05.

The researchers concluded that the modified intent-to-treat analysis, which had always been planned as part of the study and which was used throughout the study as the primary analyses to determine if the trial should be stopped on the grounds of futility, gave the most clinically useful information for making future decisions about how to take the vaccine forward, since it most closely reproduced the likely conditions in which a vaccine’s effectiveness would be judged in the field.

Vaccine more effective in lower-risk participants – effect may wane

Perhaps of greater long-term significance for the HIV vaccine field, Michael Nelson presented details of sub-group analyses which suggested that the vaccine exerted a greater protective effect in people with fewer sexual partners, although the study was not powered to produce definitive evidence on this question.

47.5% of participants were classified as low-risk, reporting one or no sexual partners in the six months preceding entry to the study and judging themselves to be at low risk. This judgement was corroborated by their answers to questions about their sexual partners; individuals with partners who were commercial sex workers, injecting drug users, HIV-positive or men who have sex with men were classified as medium or high risk. Individuals who themselves fell into any of these categories were classified as high risk. Only 24% of participants were classified as high risk.

When the vaccine efficacy was compared between the high-risk and the low- and medium-risk groups, there was a suggestion that individuals in the low- and medium-risk groups experienced a greater reduction in the risk of infection if they received the vaccine. Whereas the vaccine efficacy was 40% in the low-risk group and 46% in the medium-risk group, it was only 3.7% in the high-risk group. (Confidence intervals overlapped for all three estimates.)

Dr Jerome Kim of the US Military HIV Research Program stressed that the finding was not statistically significant and that the study was not powered to look at these questions, but said the results were intriguing.

Similarly intriguing was the trend towards a greater protective effect in the first year, indicating that the effect of the vaccine combination may wane over time.

Although strong cell-mediated immune responses were observed against HIV envelope and gag proteins in a modest number of participants, it is still impossible to determine if any immunologic parameters correlate with protection from infection, or to unpick the relative contributions of the two vaccines used in the study.

"These data need to be ripped apart by many, many people. More questions raised by the data will help the field focus on the most important studies that need to be done as we go forward," Mitchell Warren of the AIDS Vaccine Advocacy Coalition told aidsmap.

The investigators are due to launch a website submission system soon at www.aidsresearch.gov where investigators anywhere in the world who wish to carry out research on stored samples from the study can propose experiments that may shed light on what happened to trial participants and how the vaccine may have worked.

The trial investigators have also asked the HIV Vaccine Enterprise and the World Health Organization to convene a meeting with ethicists, researchers and advocates to determine whether future vaccine studies can use a placebo group or whether, given the modest efficacy of the vaccine combination used in the Thai trial, it is no longer ethical to do so in some or all future studies.

Reference

Supachai Rerks-Ngarm et al. *Vaccination with ALVAC and AIDSVAX to prevent HIV infection in Thailand*. *New England Journal of Medicine*, online advance publication, October 20, 2009.

Phambili trial of Merck vaccine shows post-infection benefit in women

By Keith Alcorn

A clinical test of Merck's adenovirus-vectored subtype B HIV vaccine that ran alongside the halted STEP vaccine trial has reported that women who became infected despite vaccination had a lower viral load set point than women who became infected in the placebo group, Dr Glenda Gray reported on Tuesday at the AIDS Vaccine 2009 conference in Paris.

However, the numbers involved were small, and the difference in viral load set points was not matched by a sustained difference in CD4 cell counts.

The Phambili study was a companion to the STEP trial, a large international study of an HIV vaccine designed to produce cell-mediated immune responses that might protect against infection, or in those infected despite vaccination, slow disease progression, therefore providing a clinical benefit.

The STEP study was halted in 2007 after the trial's Data and Safety Monitoring Board concluded that no matter how long the study lasted, it would never demonstrate a difference between vaccine and placebo groups (a statistical test called futility).

[Subsequent tests showed](#) that uncircumcised men were at higher risk of HIV acquisition if they received the vaccine compared to the placebo group, as were individuals in the vaccine group who had higher levels of adenovirus-5 antibodies due to previous exposure.

The Phambili study tested the vaccine in high-risk men and women in South Africa, and was intended as a test of the vaccine's potential for cross-clade protection. The Merck vaccine was based on HIV-1 subtype B, but the dominant subtype of HIV circulating in South Africa is subtype C.

The study was designed to recruit 3000 high-risk men and women at five sites across South Africa, but was halted when the decision was reached to close the STEP study. By this point the study had recruited 801 participants.

Dr Glenda Gray reported interim results to December 2008. At this point 90% of participants were still undergoing follow-up, and 80% of participants had received at least two vaccinations before study vaccinations were halted.

By December 2008 a modified intent-to-treat analysis that included all participants who were randomised showed that 24 infections had occurred in the vaccine recipients and 17 in the placebo group, a non-significant difference. A per-protocol analysis, which included all participants who had received at least two vaccinations, showed 22 infections in the vaccine group and 19 in the placebo group.

The infection rate per 100 person-years of follow-up was 4.69 in the vaccine group and 3.8 in the placebo group, with a hazard ratio of 1.26 (95% confidence interval 0.76 to 2.10, $p=0.37$).

Although none of the differences in infections or infection rates between the two arms was statistically significant, there were always more infections in the vaccine arm, no matter how the data were compared.

Dr Nelson Michael of the US Military HIV Research Program noted that the infection rates seen in the Phambili study were at least tenfold higher than those seen in the Thai RV144 vaccine study, conducted predominantly in a population at low and medium risk for HIV infection, and the rates reflect the very high HIV prevalence at trial sites in South Africa.

People in their early 30s (31 to 35) were at higher risk of HIV acquisition: compared to 18 to 20 year olds. They were 3.7 times more likely to become infected (HR 3.7, 95% CI 1.2 to 11.5). 21 to 30-year-olds were also at higher risk (HR 2.9, 95% CI 1.1 to 7.5).

Women were significantly more likely to become infected in both vaccine and placebo group. After adjustment for age the hazard ratio was 2.8 (95% confidence interval), and there was no discernable effect of prior adenovirus exposure or circumcision status on the risk of HIV acquisition, unlike in the STEP study.

Women in the vaccine group who became infected showed a trend towards a lower viral load set point than women in the placebo group (-0.57 log lower) in the modified intent-to-treat analysis ($p=0.09$), but the same trend was not seen in men. An

early statistically significant trend at three months towards a lower number of individuals in the vaccine group with a CD4 count below 350 cells/mm³ had disappeared by month 12.

Overall, the viral load and CD4 trends showed no significant difference, said Dr Gray, but the viral load setpoint effect in women requires further study.

Even though the vaccine was based on subtype B HIV-1 sequences, trial participants generated strong T-cell responses to HIV-1 subtype sequences as measured by ELISPOT assay.

Immunogenicity data from the first 186 participants to be vaccinated, measured at week 8 showed that among those uninfected at week 12, 77% produced a response to at least one subtype C epitope, and these were strongly correlated with the development of subtype B ELISPOT responses. Responses tended to be better in those with no pre-existing adenovirus 5 immunity.

Reference

Gray G et al. *Interim efficacy analysis of HVTN 503 / Phambili: a phase IIb test of concept trial of the MRK Ad5 HIV-1 gag/pol/nef vaccine conducted in HIV-1 uninfected adults in South Africa*. AIDS Vaccine 2009, Paris, abstract SS01-04, 2009.

Adenovirus link to HIV acquisition diminishing over time in STEP vaccine study

By Keith Alcorn

The trend towards an increased risk of HIV acquisition associated with prior adenovirus exposure in vaccine recipients in early follow-up from the STEP study seems to diminish over time, Susan Buchbinder told the AIDS Vaccine 2009 conference in Paris on Tuesday.

The STEP study was halted in October 2007 after it became apparent that no matter how long the trial continued, it was unlikely to show any difference in the risk of infection between vaccine recipients and placebo group.

However, subsequent analysis soon revealed that certain subgroups of vaccine recipients had a higher risk of HIV acquisition than placebo recipients.

Male vaccine recipients who were uncircumcised and who had antibodies to adenovirus-5 due to prior exposure had the highest risk of HIV acquisition ([see this report on earlier findings from the study](#)). The vaccine studied in the STEP trial, manufactured by Merck, used a common cold virus called adenovirus-5 to deliver multiple HIV sequences in order to stimulate cell-mediated immunity.

A number of theories have been put forward to explain why prior adenovirus exposure might increase the risk of infection, and scientists have been concerned that use of adenoviruses as a

vector for delivering HIV sequences in vaccines might pose a risk to vaccine trial participants.

Indeed, the biggest concern was that any interaction between the vaccine vector and adenovirus antibodies in vaccine recipients might place trial participants at permanently heightened risk of HIV infection.

Consequently, investigators from the STEP study have been conducting careful follow-up to assess whether new infections are occurring disproportionately in the categories previously detected to be at higher risk.

Susan Buchbinder of San Francisco's Department of Public Health presented results of follow-up on trial participants for the period from October 2007 to 23 January 2009.

A total of 60 new infections occurred in study participants between unblinding in October 2007 and January 2009. Twelve occurred in women (six in each group) and 48 in men (26 in the vaccine group and 22 in the placebo group). The higher rate of infections in men is explained by the fact that just over 60% of trial participants were men; the study recruited men who have sex with men and female sex workers in the United States, Latin America and Australia.

An excess risk is still evident in Ad5-seropositive men, but it is no longer trending towards significance, said Susan Buchbinder. In uncircumcised, Ad5-seropositive men the risk had declined too, although it remains of borderline statistical significance.

"So the question is, was this just noise? The other explanation is that the risk has just gone away over time," she said.

Dr Gary Nabel of the US National Institutes of Health Vaccine Research Center told the conference that a wide variety of adenovirus vectors, much less common in humans, are now being investigated, but that simian adenoviruses may prove less problematic as vaccine vectors.

Reference

Buchbinder S et al. *Clinical outcomes from the STEP study*. AIDS Vaccine 2009, Paris, abstract SS01-02, 2009.

about HATIP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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