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Point-of-care (POC) diagnostics are essential to achieving an AIDS-free generation and improving outcomes in HIV-exposed children

By Theo Smart

Summary

- Success in achieving an AIDS-free generation will depend on achieving consistently high performance at all steps in the 'cascade' of activities which limit the risk of HIV transmission to the child.
- Laboratory and point-of-care tests – HIV antibody tests, HIV DNA PCR tests and CD4 counts – each have a role to play in this process.
- Important innovations in laboratory tests are now beginning to become available. These tests have the potential to reduce the risk of transmission during pregnancy, delivery and breastfeeding through earlier and more efficient diagnosis and monitoring of mothers and infants.
- Good access to CD4 cell counts, and prompt delivery of results, has been demonstrated to improve the proportion of pregnant women who begin antiretroviral therapy during pregnancy.
- Many barriers to CD4 test access remain. The results of approximately half of the CD4 tests carried out never reach the people who were tested, because they must be sent away to a laboratory and then returned to the clinic, and each patient must visit the clinic again to receive the result.
- This is why it is important to develop and make widely available a new generation of CD4 test devices which can be used at the point of care, while a mother is attending an antenatal clinic, to deliver a result within an hour.
- A number of studies have now shown that CD4 testing at the point of care leads to an increase in the uptake of ART among pregnant women.
- Early diagnosis of infant HIV infection is essential due to the higher risk of HIV disease progression during the first year of life.
- Dried blood spots have been used to collect samples for testing at central laboratories, but as with other testing methods carried out at facilities remote from the point of care, the results of these tests frequently

fail to reach the clinic where the infant was tested, or the caregiver of the infected child.

- Services which achieve high rates of early infant diagnosis also achieve a high degree of integration of activities. Testing for early infant diagnosis can take place at the 6-week immunisation visit; if this visit takes place at the site where PMTCT interventions have been provided, it is more likely that results of testing of infants known to be HIV-exposed will be followed up.
- Community follow-up of mothers who do not come back to the clinic for results also has the potential to improve rates of early infant diagnosis and treatment.
- Point-of-care testing would eliminate some of the factors which cause delay and loss to follow-up. A large programme to fund and deliver new point-of-care tests for early infant diagnosis is now underway, funded by UNITAID and administered by UNICEF and the Clinton HIV Access Initiative.
- These tests will not be available everywhere immediately, so there is still a need to improve the performance of testing activities that use dried blood spots, and to ensure that all infants exposed to HIV are tracked through the health system from birth to delivery of an HIV test result, so that those with HIV receive treatment and those without HIV continue to receive prophylaxis against HIV infection.

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Introduction

A large number of reports were presented at the symposia and poster sessions of the 19th International AIDS Conference (AIDS 2012) and at its associated pre-conference meetings and satellite meetings, on the delivery of the package of services commonly referred to as the prevention of vertical transmission, or mother-to-child HIV transmission (PMTCT).

These programmes have evolved dramatically from the early HIV testing and single-dose nevirapine projects, growing in complexity, with many separate interventions cutting across disciplines, and involving a continuum of care with complementary objectives. They include:

- HIV testing, counselling and prevention services among women at risk of HIV
- The care, support and treatment of women living with HIV
- The care, support and treatment of pregnant women living with HIV
- The prevention of vertical HIV transmission within the context of family-based care and male partner involvement
- The care and management of HIV-exposed infants, including infant HIV prophylaxis
- Early infant diagnosis (EID)
- Linkage to and uptake of paediatric HIV treatment when necessary.

In the past, there has been considerable focus on the efficacy of particular antiretroviral regimens for the prevention of vertical transmission, but in recent years there has been a growing recognition that prevention of HIV infection and AIDS in children is a complex process, or 'cascade' as the sequence of services outlined above shows.

Studies and programmatic experience in some countries seem to suggest that despite improvements in the performance of some of these services, continuing sequential losses along other parts of the 'PMTCT cascade' mean that very few mother-infant pairs receive all the interventions, and very few HIV-infected infants are actually diagnosed and make it on to treatment. In addition, the focus of infant diagnosis on mother-infant pairs tends to ignore both children cared for by other family members and those who arrive at health facilities other than the HIV clinic, sick and in need of evaluation for possible HIV infection.

There are many reasons why programmes don't perform as well as they should, but one seems particularly intractable in low-resourced settings, particularly in remote areas with poor infrastructure: the poor access to reliable HIV laboratory services that serve as the gateway to antiretroviral treatment (ART) in most countries' HIV programmes. There have been multiple reports that have described how poor access to these lab services in these settings is a barrier to care.

As long as eligibility for antiretroviral therapy (ART) is determined on the basis of the result of a lab test, and if either that lab test, or the results, cannot be readily and reliably accessed in every part of the country, it may not matter how well a clinic's PMTCT programme is doing, or even whether the healthcare system overall is doing an outstanding job in addressing the performance and uptake of the most of the individual components of PMTCT.

Without maternal access to timely CD4 cell monitoring and an efficient and comprehensive system for early infant diagnosis, a country will not achieve an AIDS-free generation, and the lives of many HIV-infected infants will continue to be lost.

These gaps are likely to become more apparent as programmes continue to scale up and decentralise to primary healthcare facilities in remote rural settings.

One solution might be to no longer require CD4 counts for mothers to initiate treatment, which Malawi is doing for the mothers at least, by adopting what is called 'Option B+'—providing ART *for life* to any pregnant women who tests positive for HIV. However, although a strong case can be made that it will be cost-saving in the end, the up-front costs of Option B+ may not be judged affordable in all settings, and in any case it does not take care of either the diagnostic or the treatment needs of the child.

Another approach, and the topic of several symposia at AIDS 2012, would be to speed up the development and implementation of new point-of-care (POC) diagnostic tests that could be easily and affordably performed in less well-resourced facilities, possibly even in the patient's home, with results provided in under an hour. This strategy got a big boost at the conference, with an announcement that UNAIDS had committed US\$140 million for projects implemented by the Clinton Health Access Initiative (CHAI), UNICEF

and Médecins Sans Frontières (MSF) to increase access to affordable point-of-care HIV diagnostics adapted for use in resource-poor settings.

Acronyms

- **ANC: Antenatal clinic**
- **ART: Antiretroviral therapy**
- **DBS: Dried blood spot (used to collect blood samples for HIV DNA testing)**
- **EID: Early infant diagnosis**
- **PCR: Polymerase chain reaction, a test which detects HIV**
- **PMTCT: Prevention of mother-to-child transmission**
- **POC: Point of care**

Background on critical laboratory services for HIV management in resource-limited settings

In most resource-limited settings, difficulty accessing lab tests such as CD4 cell counts or HIV virological tests (HIV RNA or DNA PCR tests, or ultrasensitive p24 antigen tests) limits the effectiveness of both PMTCT programmes and services providing paediatric ART.

Though eligibility criteria may vary, HIV programmes across the globe have long relied on CD4 cell count measurements to determine whether adults and adolescents living with HIV, including pregnant women with HIV, qualify for treatment. Putting a pregnant woman with a CD4 cell count below 350 onto ART not only reduces her risk of falling ill or dying, it also reduces the risk of HIV transmission to her infant and increases the likelihood of her children (both HIV-infected and uninfected) surviving.

Infants may become infected *in utero* early during pregnancy, so a woman with HIV already on an effective ART regimen when she becomes pregnant is less likely to pass on the infection—as long as she is adherent to treatment and her virus remains suppressed—than a woman who starts ART only after she learns she is pregnant. Similarly, the earlier in pregnancy that ART is commenced, the lower the risk of transmission at the time of delivery, since a longer period of treatment provides a greater opportunity for viral load to be fully suppressed at the time of delivery.

Access to viral load monitoring could improve outcomes in both cases. Programmes that can provide viral load monitoring would be able to determine whether a woman's viral load is suppressed, and whether it continues to be so prior to delivery. Access to viral load test results could also assist women in HIV serodiscordant relationships to conceive more safely, by detecting if the HIV-positive partner's viral load is truly suppressed, thereby decreasing the risk that the HIV-negative partner might be exposed to HIV while the couple is attempting conception.

HIV laboratory services are also critical for the management of HIV-exposed infants; symptom screening for the determination of HIV infection is not adequate.

Although it may have some use in older children, [recent evidence suggests that using a 'symptom screen' for HIV, namely the WHO IMCI algorithm for HIV diagnosis, is less useful when applied to infants](#), especially where information on infant exposure is lacking.¹

Ruslan Malyuta of UNICEF notes that the critical issue driving under-performance of the algorithm is the lack of information and documentation regarding HIV exposure. Application of the IMCI algorithm for children with known HIV exposure, with no ARV prophylaxis during pregnancy, delivery or breastfeeding, could be of use. In the absence of diagnostic tests, treatment can be initiated and HIV status can be reviewed at 18 months of age; [if the infant tests negative further investigations will be needed](#) to determine whether the child is uninfected or whether negative antibody status is a consequence of very early viral suppression by antiretroviral treatment.

Methods of infant diagnosis

Any HIV-infected infant below the age of two qualifies for immediate ART but early infant diagnosis (EID) requires specialised testing. Since young HIV-exposed infants may retain maternal antibodies to HIV for up to 18 months after birth, conventional or rapid antibody tests cannot determine an infant's HIV status—but a positive result is nevertheless useful because it indicates that an infant is HIV-exposed.

Only laboratory tests that can detect the components of the virus itself, either nucleic acids (HIV RNA or DNA PCR) or antigens (ultrasensitive p24 antigen tests) can diagnose HIV in infants.

At present, virological tests can only be performed using expensive equipment in technically advanced laboratories, usually installed only in large referral hospitals or centralised laboratories in major cities—though specimens can be sent to these facilities for testing (but that can also be problematic in settings with limited infrastructure).

Similarly, CD4 cell count monitoring is supposed to be integral to HIV care and management and there have been great efforts to make it more widely available, for instance, at ART sites in smaller hospitals and larger clinics, but it is not currently available at the primary healthcare level in most countries.

It is important to remember the setting. Africa is a vast, rich, dynamic and diverse place. However, it is a fact of life that resources and services are not equitably distributed and certain types of infrastructure, such as a paved road system, are less developed in some regions, and could be virtually absent only one hundred kilometres away from gleaming cities.

This is one reason why interventions that might work very well in one part of the continent (or country or province) may be impractical in another, and why a range of different diagnostic solutions will be necessary. Laboratory services for HIV diagnosis and monitoring are a case in point. Conventional heavy lab technology can be implemented more readily in a middle-income industrialised country such as South Africa.

The impact of laboratory services on vertical transmission

Access to good laboratory services in South Africa may be an unappreciated but critical element in the dramatic turn-around of its PMTCT programme reported in 2011 at the 5th South African AIDS Conference, and IAS2011 in Rome.² PMTCT programme performance was very disappointing, so fixing the programme had been given a high priority in the national strategic plan. South Africa updated its PMTCT regimens and ART eligibility criteria, increased its service coverage and tried out interventions to increase uptake, decrease losses to follow-up and improve turnaround times at each step of the 'cascade'.

Two years later, a surveillance study was conducted utilising dried blood spot (DBS) specimens from 10,000 babies delivered between June and December 2010, using samples taken at 580 facilities across South Africa's nine provinces. 31.4 % of the infants were HIV-exposed, of which 3.5% were HIV positive (compared to around 20% a couple of years earlier in a study in KwaZulu Natal province).³ In just two years, South Africa had dramatically reduced perinatal HIV transmission and saved an estimated 67,000 infants from becoming infected during that period.

Subsequently a cross-sectional study published in the *WHO Bulletin* in March 2012 provided independent verification of the surveillance study's findings.⁴ Horwood et al. looked at the provincial PMTCT programme in KwaZulu Natal about a year before the surveillance study, and reported highly consistent findings. The frequency of HIV transmission to exposed infants at six weeks after birth in KwaZulu Natal during this period was 7.1%, a 66% reduction from the 20.2% prevalence reported earlier. (What we don't know is what proportion of these infants subsequently tested positive—or were ever re-tested—which are the ultimate markers of the performance of the programme.) The researchers attributed the success to a few key factors:

- The high uptake of HIV testing—more than 90% of the women in the programme either tested during their pregnancy, or already knew their HIV-positive status
- A seamless switchover to the new ARV regimens
- Importantly, in comparison to the previous period, good access and high uptake of CD4 cell count testing.

In respect of the final point, the authors note that 79.9% of women received a CD4 cell count, and of these, 83.5% obtained their result (pretty high considering that a number of women only present for antenatal care late in their third trimester, and their CD4 results don't always get back in time to be collected before delivery). 22.1% qualified for ART, and 69.3% of those were taking it at the time of the interview. These rates of uptake are generally much higher than in most sub-Saharan African countries.

"Our findings show that, in the province with the highest HIV prevalences in South Africa, low rates of mother-to-child transmission at population level were achieved within a short period of more effective regimens being implemented," Horwood et al. wrote. "This major accomplishment for the provincial health authorities should be feasible elsewhere."

Note again, that this study was conducted before the CD4 threshold for initiating ART was increased to 350, yet outcomes were already improving. Another study, conducted at Prince Myshyeni Hospital in Umlazi (near Durban) just prior to the national surveillance study and still under the previous South African policy for the management of pregnant women with HIV with a CD4 count below 200, found a three-fold higher incidence of *in utero* HIV transmission among women with a CD4 count below 200 who did not receive ART.⁵

Even after the CD4 cell threshold eligibility changed, there were concerns about not getting the results in time in many primary care sites, and nurses feeling confident to prescribe ART. "The quality of the PMTCT programme varied across provinces," said Dr Ameena Goga who reported the results of the nationwide surveillance study. "Consequently, these results will be shared with each province to show them where there are gaps in their service delivery—such as a failure to provide CD4 cell testing and deliver the results in a timely fashion, failure to get those women who qualify onto ART."

But access to CD4 cell counts has been steadily increasing in South Africa, which has one of the world's leading reference

laboratory systems, with hundreds of district and peripheral nodes stretching across the nine provinces. Being able to provide CD4 cell measurements is a major advantage in terms of getting women who qualify for treatment onto ART, and since they have the highest risk of transmitting the virus without treatment, this can have a disproportionate impact on programme outcomes.

Speeding up access to CD4 test results

Dr Chioma Nwuba of Management Sciences for Health said this was what just happened for a laboratory strengthening and task-shifting project in Kwara State, in northern Nigeria, during an oral abstract session at AIDS 2012.⁶

“In some developing countries, [CD4 cell monitoring] is only available once a week on clinic days making it difficult for persons who test positive on non-clinic days to have access to baseline CD4 estimation,” she said. “Long waiting time coupled with the burden of travelling long distances to and from clinics for initial blood draw and receipt of CD4 results has led to attrition in the number of clients who test positive to HIV versus the number who eventually commence ART.”

Furthermore, there weren't enough healthcare workers to attend to the patients, and already overburdened doctors were being asked to fill out laboratory and pharmacy request forms before patients could get their CD4 cell counts or ART, before accessing laboratory investigations or collecting their antiretroviral drugs.

So several interventions were implemented including task shifting the paperwork to clerks, and providing CD4 cell testing every weekday. They established a policy that everyone who tested HIV positive would be able to have blood drawn for CD4 cell counting on the same day and receive results within 24 hours. They synchronised patient appointments with pharmacy and lab services so that patients wouldn't have to make multiple unnecessary trips.

After just twelve months, “the number of HIV-positive clients who accessed baseline CD4 investigations at our HIV care and treatment clinic increased from 53.8% to 93.3%. In addition, the number of pregnant women placed on antiretroviral therapy increased from 50% before the initiation of our interventions to 83% after the interventions. Furthermore, the number of patients lost to follow up reduced from 58.7% to 10.7% by the end of twelve months,” she said.

The average client waiting time on clinic days dropped from 4 hours to 90 minutes, which increased patient willingness to come in for care, and reduced the laboratory turnaround time for CD4 cell counts from 7 days down to 24 hours, which led to more rapid initiation of eligible patients on antiretroviral therapy.

Not every facility can have CD4 cell testing equipment on site however. Ever since the start of the ART rollout in resource-limited settings, implementers have grappled with ways to make these laboratory services more widely accessible in more remote settings. For instance, HATIP #69 reported how, in the early years of PEPFAR, funding was provided to some partners to set up a sample referral system for CD4 monitoring. In Zambia, USAID provided the funding for motorcycles and cooler boxes to transport samples on specified days from the outlying clinics to referral laboratories set up in strategic areas with CD4 cell monitoring equipment.

Lack of access remains a fundamental problem

In the years since, less expensive and complex CD4 monitoring machines have been developed, and were supposedly widely implemented to support ART programmes. However, even though CD4 cell monitoring is supposed to be widely in place, it isn't always

reliably accessible, and it may not be possible to get the results in a timely manner, according to representatives from civil society and national networks for people living with HIV from across sub-Saharan Africa attending a meeting of the Leadership Through Accountability Programme, held in Johannesburg, South Africa in June 2012. Participants had been asked about their access to laboratory monitoring, and their answers were more than a little shocking. (The following dialogue has been adapted from the meeting report, which is in press.)

Two activists from Tanzania said there was intermittent access to CD4 cell tests in the government facilities. Even though the policy was to provide people living with HIV with a CD4 cell count every six months, it could actually take as long as two years. When they were asked why, they responded in unison “The machines are out of order.”

“A lot of districts don't have CD4. They've got the machines but they don't have the reagents,” said an activist from Senegal. Another said it was similar in Cameroon, and that since Global Fund support for the laboratory services had ended, many patients now have to pay for the test.

“In Ethiopia, there is CD4 coverage in the big cities, but the accessibility for CD4 for rural villages and the rural towns is very difficult, they have no access to transport, they are expected to travel far distances, they have transportation problems,” said one activist.

“In Kenya, there is access to CD4 count, but with difficulty, in terms of travel,” said another, “usually in facilities which are supported by partners, and donors such as MSF. Even when it's in the government facilities, it is supported by partners e.g. MSF. Then there may be no reagents and there may be frequent breakdown of machines. Like in the Rift Valley—which is a very big province—there is only one machine situated at the provincial hospital, and most of the time it is not in working order.”

Even where the tests are available, complicated logistics between getting the blood drawn and sent to the lab and then getting the results back provides opportunities for many things to go wrong.”⁷

Poor access to CD4 counts acts as a barrier to treatment for many individuals. To illustrate the point, at AIDS 2012, there was a poster on early infant diagnosis in Tanzania, in which the researchers bemoaned the fact that a low percentage (14.6%) of the mothers with HIV in the cohort were on ART.⁸ How many were eligible for treatment? Who knows? There was no information about CD4 cell counts in anyone's register.

This suggests that CD4 counts are not even being offered, which may be tantamount to a human rights violation, since it is required to access ART.

Virologic testing technology is even more difficult for resource poor settings to install and maintain ([see this resource](#) on the infrastructure required). So what is the work-around solution for early infant diagnosis? Collecting and drying blood spots (DBS) samples from infants, when they'd be likely to access health services: such as their first visit at an immunisation clinic. The DBS specimens could then be sent to a centralised referral lab where the equipment to do virological tests for HIV had been installed.

Applying these workaround solutions like this and others—such as couriers on bikes so that pregnant women with HIV attending the antenatal clinic could get their CD4 cell counts to see if they qualified for ART, or when they've become mothers, to find out whether their infant is HIV-infected and in need of immediate ART—could work in some cases, but they also introduce a number of steps or interactions with the health services into the ‘PMTCT

cascade', and more opportunities for things to go wrong. The process also takes time, especially dried blood spot for early infant diagnosis, when it is a very precious commodity.

There is little time to waste when an infant has HIV

Without treatment, many infants with HIV don't have much time at all, especially in a resource-limited setting, where their risk of death is particularly high, as various presentations at recent conferences have shown.

For instance, in Blantyre, Malawi, HIV-infected infants have at least a five- to eight-fold higher rate of death compared to uninfected children according to an analysis of data from over 8000 mother-infant pairs, presented as a poster at AIDS 2012.⁹ The rate of death is probably worse than that, because Malawi didn't have access to HIV DNA PCR tests.

Furthermore, "The youngest children have the highest death rates," wrote the authors of a poster describing a paediatric cohort from an MSF-supported facility in Zimbabwe,¹⁰ and this was confirmed by the researchers doing similar studies in other parts of Africa.^{11,12,13,14}

This isn't news. It has been depressingly clear since the virus was first discovered, and before treatment was available, that HIV disease has an early onset and rapid course of progression in many infants. Roughly 40% of HIV-infected children die before they reach their first year of life.¹⁵

"Mortality of HIV-infected African children is higher at lower ages, especially below two years of age," said Dr James Nuttall of the Red Cross Children's Hospital and University of Cape Town at the 7th Annual Paediatric AIDS Treatment for Africa (PATA) Forum. Held last November, in Gaborone, Botswana, the PATA meeting had an entire day devoted to early infant care.

An HIV-infected infant can also be in seemingly good health, with high CD4 cell counts or percentages that belie their risk. "CD4 percentages and counts are less predictive of mortality and disease progression in younger children," said Dr Nuttall. (This partly explains why symptom screens aren't sensitive enough to diagnose HIV in young infants.)

An HIV-positive child's condition can suddenly turn. Their first illness is often their last.

"Young infants with HIV are fragile, when they get sick. They can progress rapidly to death, and the mortality rate is high. In the Children with HIV Early Antiretroviral Therapy (CHER) study, most of the infants died within the first six months," said Dr Shaffiq Essajee of the World Health Organization, who gave a plenary talk on 'Fast tracking infants on to treatment' at the PATA meeting.

However, the CHER study, published back in 2008, also found that starting antiretroviral therapy before 12 weeks of age reduced early mortality by 75%.¹⁶

CHER's results appeared to mark a watershed moment. It led to a WHO recommendation that all children living with HIV under the age of two should receive ART.

But its impact so far in terms of lives saved? Less than one would have hoped. And why?

"Only 28% of children under the age of one, living with HIV, are accessing ARVs," said UNICEF's Dr Chewe Luo, during a press conference at AIDS 2012.

The UNICEF Stocktaking Report suggested that numbers of HIV-positive children on ART has been growing, along with ART rollout over the last several years. But as Dr Nuttall pointed out, the children going onto ART are usually much older, according to data

from the leDEA collaboration (which includes data from over 25,000 children with HIV in 13 Southern African cohorts). In 2010, the median age for a child to be put on ART at these sites was four years old (interquartile range: 16-106 months).

A number of posters at AIDS 2012 describing efforts in different countries trying to boost the number of infants on treatment made the same observation—most of the new children starting were older than infants. This was described in one poster reporting on an MSF-supported clinic in Bulawayo, Zimbabwe, where there was a concerted effort to implement early infant diagnosis (EID), and get infants onto ART as early as possible. Again, the age of the children initiated on ART was much older. Even the children who were referred directly to the treatment programme from the PMTCT site were older than one would expect when they began initiating ART: 1.2 years of age.¹⁷

"Even for [infants referred from a PMTCT programme] median age at initiation was still too high to maximally improve survival," the authors wrote.

This means that most of the children at greatest risk of dying without treatment simply didn't get it, with predictable results. The older children presently initiating ART are the 'survivors', a fraction of the children with HIV who were born the same year. The tip of the iceberg with most of the rest, buried.

It may sound like circular reasoning, but to save more lives, HIV-positive infants must be identified and put on treatment as soon as possible, before they die.

"The median age of ART initiation in CHER was 7.4 weeks," said Dr Nuttall before posing a question that would be the subject of subsequent group discussions at the workshop: "Could we achieve that in routine clinical practice? How?"

How can programmes achieve earlier diagnosis?

Programmes and teams have certainly been trying to achieve earlier treatment initiation in infants and children — there are a lot of innovations, and best practices that studies show do help, sometimes profoundly. But many of the studies presented at the PATA meeting, at CROI 2012 in Seattle, in the medical literature and at AIDS 2012 this year suggest that it won't be easy, not with the tools programmes currently have available.

"Despite improvements in the prevention of [vertical] transmission programmes and infant testing coverage, many women and infants are not getting tested and are lost to follow up, resulting in high infant and child mortality," said Dr Essajee at PATA.

"There is very little access to testing for children living with HIV in resource-limited settings," Dr Luo said at AIDS 2012. "So we don't know where they go. And if we don't treat as many of the children as possible within the first few months of life, 50% will have died."

She places a lot of the blame on the expensive laboratory technology poorly suited to setting, and to the 'work-around solution' proposed to help provide access to early infant diagnosis: dried blood spot sampling.

"A few years ago, we thought that dried blood spots for early infant diagnosis would be a game changer, but its delivery is awfully complicated," Dr Luo said.

"A few years ago, we thought that dried blood spots for early infant diagnosis would be a game changer, but its delivery is awfully complicated." Dr Chewe Luo, UNICEF.

Dried blood spots (DBS) make it simple to transport the specimens without refrigeration to a central laboratory equipped to carry out HIV DNA PCR testing, and allows the range of sites at which sampling for early infant diagnosis can be carried out to be expanded. In many countries, immunisation clinics have now been tasked to perform specimen collection for EID during the child's first immunisation visit. However, so far, only about 2% of HIV diagnoses are happening at immunisation clinics.¹⁸ Many still only take place once children present sick to health facilities such as under-5 baby clinics — one reason why older children are more likely than younger children to access ART. The problem may be that early on, sampling blood for EID at immunisation clinics adds several more links to the PMTCT cascade.

It depends, first, on the awareness of the mother that the child is HIV-exposed and in need of testing and her subsequent ability to bring the child in for testing, either back at the PMTCT site, or between four and six weeks after birth, to attend the immunisation clinic where a dried blood spot can be collected, or to agree to EID while there. This involves pricking each child's heel, collecting a spot of blood on a filter paper card, which is then placed somewhere for several hours to dry. Then the labelled specimen is placed in an envelope, until enough children come into the facility, and enough DBS specimens have been gathered to send into the lab by courier or post.

When the lab gets the specimens, they will be tested whenever the lab technicians get to it, which depends on their workload at the time. Then the test itself takes a while to run. When the results are ready, the lab is supposed to send them to whomever is managing the patient, who in turn will need to get the results to the patient.

But since the test needs to be run on batches of specimens to be more cost-effective, some specimens may wind up sitting and waiting, potentially for weeks, until there are enough others to justify using the equipment. Dr Essajee pointed out that this makes it difficult for the healthcare provider to predict when the results will be ready and when to advise the mother or caregiver to return to the clinic.

In the early days of DBS rollout there were horror stories of test results taking months to arrive—sometimes delivered to grieving mothers. And perhaps even more often, the mother or caregiver never came back for the result.

So a few years back, UNICEF organised a major five-country evaluation of DBS for EID, how it was being used, and whether it led to better outcomes. They found that losses to follow-up occurred all along the EID cascade. A lot of money had been spent, but very few HIV-infected infants were making it into care and onto ART. Instead, they would become lost to follow-up somewhere along the EID 'cascade'. About 51% of the test results were never collected.

This is something that particularly concerns Bernhard Schwartländer, the Director of Evidence, Innovation and Policy at UNAIDS.

"Patients do not get the results. Roughly half of all laboratory-based CD4 and EID results are never delivered to patients," he said during one of AIDS 2012's several sessions on point-of-care (POC) diagnostics. He presented a graph based on the weighted average of data from sub-Saharan African countries, suggesting that at least 46% of CD4 test results are never received by the patient. Given the investments that have been made, this represents a huge waste.

Dr Zach Katz of the Clinton HIV Access Initiative pinned a dollar figure on this wastage: "almost six million test results never reach the patient at a cost of around US\$60 million a year," he said.

One should rather say that the results are not 'delivered' to the patient. Since getting the results back can be so unpredictable, it would seem important for someone to be keeping track of the family. But the immunisation clinics rarely provide follow-up, or deliver results. This is often a somewhat awkward moment for many health services: when the mother-infant pair is in a sort of health system limbo, no longer really the responsibility of the antenatal clinic and not yet engaged with the paediatric ART service either. Dr Essajee pointed out the immunisation clinic is just a brief stopover where the child has his or her heel pricked so that a dried blood spot can be collected for early infant diagnosis. Immunisation clinics really don't do much more than immunise. Taking on EID is a new task for them. Since it is not where the child will be receiving treatment and the personnel may not see what becomes of the child as their responsibility, Dr Essajee said he feels the paediatric treatment sites (which are far fewer in number) have a responsibility to network, and monitor the immunisation clinics and actively participate in keeping the families in care, but this rarely happens in practice.

So the time it takes between having blood drawn and getting the results back varies, and the healthcare worker may have told the mother to come back weeks too early.

"Mothers often return to the clinic, to learn that results are not ready, and this results in a loss of confidence in the system," said Dr Essajee.

New data in the field

But a long turnaround time translates into delayed treatment decisions, which could have deadly consequences.

"The turnaround time for results of DBS samples was often long—four to twelve weeks—at our facility and caused delay in decision making regarding infant care and follow up," said Dr Abdurraheem Abubakar, of the Management Sciences for Health's ProACT Project in Kwara State, Nigeria. ProACT is a project that provides technical assistance, and works to develop capacity for health in targeted states in Nigeria.¹⁹

He presented a poster at AIDS 2012 describing the effort to introduce EID to PMTCT services at two hospitals in the state, and told HATIP that the "long turnaround times affect paediatric HIV diagnosis and access to life saving ARVs in most resource constrained settings."

Reasons for delays

The problem was subsequently investigated by a national task team on PMTCT which identified several reasons why the turnaround times were so long and unpredictable:

- The courier services and transport logistics were inefficient
- The facilities weren't really set up to perform the service, with inadequate and congested workspace for EID services, which affected packaging of samples
- Facilities had irregular supply of DBS commodities and reporting tools
- There were inadequate staff and increased workload at the regional labs where these samples are analysed.

However, other teams have had better outcomes implementing EID programmes. Needing to screen infants for HIV as part of a clinical trial evaluating stunting and developmental complications in children living with HIV in Malawi, Dube et al. recently reported a particularly impressive job integrating EID into a primary care setting—achieving 71.6% EID coverage for children born to mothers

in the PMTCT programme.²⁰ Some elements of their EID process were slightly different however. One factor in their favour was that the reference lab was in the same town as their health facility, and the researchers simply drove to the lab and dropped off specimens themselves. Also, they set up sample collection during an immunisation service visit they provided directly at the PMTCT site, retaining responsibility for the mother-infant pair. Thus the clients had more continuity in care and saw the 6-week immunisation and EID testing as being part of the package of services provided by the PMTCT site. The team was well funded, well enough that they could pay for community health workers to trace cases who were lost to follow-up. Because of this, they were able to deliver HIV test results to the families of 87% of the infants who were tested.

Characteristics of a service achieving high rates of early infant diagnosis

- Immunisation visits take place at the PMTCT site in order to maintain oversight of the mother-infant pair
- EID testing takes place at the immunisation visit
- Tracing of mother-infant pairs lost to follow-up by community health workers
- Reference laboratory located in the same town; rapid delivery of specimens
- Stringent quality control of testing procedure to ensure accuracy of results
- Enough funding to employ the relevant staff to deliver the service efficiently

Nevertheless, the team complained about what they felt were shocking ongoing losses to follow-up. They had an unexpectedly high percentage of false positive results on EID. Further investigations indicated that laboratory contamination, resulting from the manual manipulation of the sample cards, was the most likely cause of the low specificity. "This observation underscores the need for stringent quality control and confirmatory testing," wrote Dube et al. This increased the cost of offering EID. It also could have further delayed treatment, but knowing how long it would take to confirm test results, they put all the initially positive children on treatment, discontinuing it once a negative result came back in. "Knowing the overwhelming benefits of early ART, we did not withhold such treatment until the confirmatory results were available," they wrote.

Moreover, they attributed much of their success to being better resourced than most clinics would be in the setting, and said that their experience would not be that easy to reproduce on a budget.

Dr Erik Schouten, of Management Sciences for Health (and the initiator of the Option B+ approach in Malawi) reported on the implementation of EID at 53 randomly selected immunisation clinics in four districts in Malawi, screening all infants attending the clinics first for HIV exposure using an ELISA test, and then screening the specimens that tested positive for HIV exposure with HIV DNA PCR.²¹ Consequently, they identified an additional 207 mother-infant pairs among women who had never been tested or who tested HIV-negative before or during the pregnancy—a 37% increase. However, while the findings of the study are useful for surveillance purposes, there was no mention of turn-around times, and how or whether these results affected patient management.

A previous report from Malawi suggested that offering EID through immunisation clinics increased the rate of HIV testing and returns for test results as compared to testing through the under-fives clinic, which sees slightly older and predominantly sick children. However, this was not a randomised study, it was a head-to-head comparison of two urban clinics, and they may not be generalisable, even to similar clinics in Malawi.

Another study in Malawi of which Dr Schouten was a co-author, presented as a poster at AIDS 2012, was less upbeat.²² The poster described a retrospective PMTCT cohort study in Zomba district, comparing child mortality and health outcomes of children by HIV-exposure and infection status at 20 months under operational conditions. The researchers had previously reported very poor uptake of PMTCT services, with only 19% of women screened for HIV at the antenatal clinic making it through each step in the cascade to present with their infant for EID.²³ Notably out of the 15 (13.5%) HIV infections identified among the HIV-exposed children who survived up until 18-20 months, only 28% had been brought in for early infant diagnosis testing (EID) at their immunisation visit. In fact, the percentage of the HIV-infected children who were brought in for EID was probably higher, when one considers the deaths: 20 or 12.8% of the cohort had died by month 12, and 32 or 18.7% of the cohort by 18-20 months. The risk of child death was three times higher in HIV-exposed children than HIV-unexposed ($p=0.03$), and it is likely that a large percentage of the children were HIV-infected. It is unclear how many mother-infant pairs who did follow-through with EID actually received the results—only two of the children were receiving ART at the start of the study.

So indeed, as Dube et al. reported, while implementing EID in this setting was feasible, it was "challenging, even when well supported by research funds. Our experience suggests that, to maximize the benefits of early infant HIV diagnosis programmes, a simple, affordable and highly specific point-of-care (POC) test for infant HIV diagnosis and better linkage to care are both needed."

Can point-of-care testing improve early infant diagnosis rates?

To test this hypothesis, another team of researchers in Malawi conducted a study, looking at how many HIV-infected children would be enrolled onto ART if they were diagnosed with point-of-care HIV DNA PCR (or as close as the researchers could get to point of care) compared to cases diagnosed clinically, using the WHO clinical algorithm for HIV diagnosis in children.²⁴ The study involved hospitalised children and for the clinical symptom screen, this meant the algorithm was better at detecting HIV than when it is used in asymptomatic children with HIV, but it was also less specific, falsely identifying numerous sick children as HIV-infected, who were then put on treatment. The 'POC' PCR test just involved the installation of PCR equipment at the hospital. Sample processing was expedited so that the turn around time was only two days, meaning that ART could be started while the infants were in the hospital.

This worked much better than standard EID with PCR in Malawi, which has a standard turnaround time of over one month. The researchers reported that 80.9% of the infants identified with 'expedited/POC PCR' initiated ART within one month of follow-up. The clinical algorithm missed about half of the HIV-infected cases, and thus had placed a substantially lower proportion of HIV-positive infants onto treatment, and a higher number of infants it falsely identified as HIV-positive onto ART (28.9% of all the HIV-negative patients). Conversely, no HIV-negative infant was started on treatment in the PCR arm.

“POC HIV virologic testing will greatly improve paediatric HIV care when more widely available,” the authors concluded.

Is six weeks the right time to test?

Other concerns about the currently recommended protocol for EID were voiced during the CROI meeting in Seattle earlier this year, in a presentation made by one of the pioneers in the field, Dr Gayle Sherman of South Africa's National Health Laboratory Service.²⁵

“Six weeks may not be the right time to be testing,” she said. “Testing at this time, delivers diagnoses a bit too late to take full advantage of lifesaving benefits of early antiretroviral therapy (ART) for an infected infant.”

She believes that the profound reduction in infant mortality seen in the CHER study may have largely been due to when ART was initiated in that study – which was around seven weeks of age in the immediate treatment arms of that study. Judging from the death records in South Africa, she said that there is a peak of early infant mortality at around 8 to 12 weeks of age.

“If we test at six weeks of age, in general children get results by ten weeks of age and are hardly ever initiated on ART before 12 weeks of age—a little bit late” she said.

Other changes in the field could lead to a re-evaluation of HIV screening at six weeks of age. New more sensitive virological testing technology can detect most HIV infections, aside from intra-partum infections, at childbirth, possibly more than can be detected at six weeks of age (given the low uptake of EID at six weeks), according to some of her own lab's unpublished data.

“Even though testing at birth would have missed the intra-partum infections, it would have detected more infections,” she said. “With the new assays we could detect 76% of all early infections at birth. And we also need to consider that these in utero-infected infants may well be those who are the rapid progressors, who need to initiate ART earlier. Added to that, if we had identified them at birth, we could have spared them the daily dose of nevirapine which would have almost certainly made them resistant to the drug.”

Indeed, this is a potential downside of the current WHO guidelines to prevent HIV transmission to infants exposed by breastfeeding—while daily nevirapine for the duration of breastfeeding protects exposed uninfected infants, it poses a serious risk of resistance for any HIV-infected child taking it, leaving little option for treatment other than lopinavir/ritonavir in most resource-limited settings.

What is less appreciated however is that prophylactic regimens, such as daily dosed nevirapine, may also affect the *accuracy* of tests used for EID. In a study Sherman conducted, a single dose of nevirapine can lead to HIV-negative results at week two in infants who tested HIV positive at delivery. These infants tested positive again at week four. “It's highly possible—or probable—that daily-dose nevirapine is going to extend the time that it takes to detect intra-partum infection. In other words, it will delay detecting those infections *beyond* six weeks of age,” she said.

This risk of infants having a false negative test result due to infant prophylaxis, which would then cause drug resistance if prophylaxis was prolonged on the mistaken assumption that the infant were HIV negative, makes the case for screening at childbirth even stronger.

“Possibly the better time to be testing is at birth; and possibly in some instances, this is the place for a point-of-care instrument, and where, if you could diagnose a child at birth you may have a better chance of retaining them in care,” said Dr Sherman.

Point-of-care testing for early infant diagnosis

Indeed, point-of-care testing for early infant diagnosis (POC EID) would be the best solution for the more remote clinics, which are not currently well served by dried blood spot (DBS) EID. The same is true of pregnant women who cannot access CD4 tests in time to go onto the best option for her and her children's health. This inequitable access to the standard of care cannot be allowed to go on.

“Universal access requires point of care testing,” said Dr Gottfried Hirschall, head of the HIV/AIDS Department at WHO, during the Pangaea Global AIDS Foundation pre-conference symposium on point-of-care diagnostics.

“In low-income settings, access to laboratories is limited. It is time to bring laboratory technology to the people—make them available at the point of care. As staff that will use them will not be laboratory experts, the technology has to be simple and robust. And it is essential that those technologies be affordable,” he said.

With a [huge grant from UNITAID, UNICEF, the Clinton HIV Access Initiative and MSF have committed](#) to speed the development of point-of-care tools (EID and CD4) that are simple enough for a nurse to perform at a primary care facility, or so that a trained home-based care provider can deliver the service in the home.

There are already a number of candidates. “Many of these assays have already performed well when assessed against their laboratory counterparts, and have been assessed in the field as well, but at present none of them have been launched,” said Dr Sherman last March (referring specifically to EID).

Point of Care tests for EID	
POC HIV NAT assays	<ul style="list-style-type: none"> o Liat HIV Quantitative assay (IQuum) o Clondia (Alere/Inverness) o SAMBA (Helen Lee) o NW RT-PCR-assay
POC p24 AG assays	<ul style="list-style-type: none"> o Ultrasensitive p24 Ag (NW University)

Timeline for introduction of new assays for early infant diagnosis and viral load testing			
2012	2013	2014	2015
Liat	Lynx EID Alere Q WAVE 80 EOSCAPE SAMBA VL	NWGHF VL SAMBA EID Cavidi AMP	Gene Xpert Lumora Micronics; ALL; Biohelix

Reproduced from a presentation by Dr Maurine Murtagh at ‘The Decade of Diagnostics’ satellite meeting, 24 July 2012, AIDS 2012.

According to Dr Hirschall, an expert panel convened in Geneva recommended that WHO first focus on increasing access by deploying POC CD4 technology at lower levels in the health systems, and develop the new tests currently in the pipeline as quickly as possible. However, they suggested that WHO increase EID testing and viral load determination: the recommendation was to use dried blood spots and central labs for now, but to develop POC technologies as soon as possible.

There are already a number of POC CD4 cell platforms on the market — HumaCount CD4 NOW (formerly PointCare NOW), the

Partec mini-CyFlow and the Alere Pima CD4 Test — and more are coming. Other experimental platforms on the horizon include: Daktari, mBio and BD platforms as well as disposables from Zyomyx and Omega Diagnostics.

Each POC test is different of course, and their relative clinical utility and cost-effectiveness will need to be determined in the field. Some of the features of each of these are compared in [this PowerPoint presentation](#).

Does point-of-care CD4 testing improve access to ART?

Studies of some of these POC CD4 tests have shown that having CD4 cell counts available on the same day that the patient presents at clinic does improve the uptake of key services.

In Southeast Uganda, the Pima POC CD4 cell test was provided to participants testing HIV positive during a five-day, multi-disease campaign, offering diagnostic, preventive, treatment and referral services in May 2011. Out of 6300 residents, 2323/3150 (74%) adults and 2020/3150 (69%) children participated in the campaign. Of the adults tested for HIV, the HIV prevalence was 7.8%, with 46% of HIV-infected adults newly diagnosed—39% of whom were successfully linked to care.

CD4 cell counts were obtained in 167 (93%) HIV-infected adults and the median CD4 count was 415 (IQR: 281–568) cells. When looking at those not already on ART, the new HIV diagnoses had a higher median CD4 count (449 cells [IQR: 281–592]; n=77) than prior diagnoses (345 cells [IQR: 279–521; n=28], though the difference was not statistically significant (p=0.28).

The programme prioritised linking those with low CD4 cell counts to care: In this subset, 83% were linked to care and started ART within 10 days. New HIV diagnoses were significantly less likely to link with care with increased point-of-care (POC) CD4 count (unadjusted OR: 0.80 for every 100 cell increase in CD4 cell count, 95% CI: 0.64–1.00; p=0.048); this association remained significant after adjusting for age, sex, and distance from clinic (adjusted OR: for every 100 cell increase in CD4 count, 95% CI:).²⁶

Provision of POC CD4 cell testing led to increased uptake of ART among pregnant women attending nine health facilities that had been outfitted with the test in Gaza Province, Mozambique. ART initiation rate was greater (p< 0.05, Kruskal Wallis) in facilities with point-of-care CD4 testing, with a relative increase of 111% (16.1%±11.6 to 33.9±18.1) compared to 72% (14.2%±6.2 to 24.4%±10.7) in facilities without POC.

Further data from a separate study in Mozambique also show that provision of POC CD4 cell testing halved the median time between HIV diagnosis and treatment initiation, from 48 days to 20 days, and patient access to the initial CD4 cell count result increased from 57% to 93%.²⁷ However, independent evaluation of the performance of the PointCare NOW assay used in this study found that when compared to CD4 counts derived from standard flow cytometry, the point of care device overestimated CD4 cell counts by 35%, with the greatest over-estimation occurring in that group of patients most in need of accurate CD4 data, those with CD4 cell counts below 350.²⁸

A couple of presentations at AIDS 2012 described Elizabeth Glaser Pediatric AIDS Foundation support for a rapid rollout of Zimbabwe's new national PMTCT programme based on the WHO 2010 PMTCT guidelines using Option A. EGPAF's support included deploying 50 point-of-care (POC) CD4 analysers to select high-volume antenatal care sites to prioritise screening of pregnant women with HIV for antiretroviral therapy (ART) eligibility in

maternal, neonatal and child health (MNCH) units. This doubled the uptake of ART by ART-eligible women in 2011 (from 2498 (17%) in 2010 to 5890 (37%) in 2011.²⁹ According to an updated oral presentation, over the period July 2011 to March 2012, 64% of eligible women initiated ART.³⁰

But will any of these tests truly be a game changer? Dr Maurine M. Murtagh (of the Murtagh Consulting Group) says it is far too soon to say.

"Essentially what we're asking a number of these point of care diagnostics to do is to compensate for relatively weak healthcare systems in-country," she said. And that may be asking too much.

"What we're asking a number of these point of care diagnostics to do is to compensate for relatively weak healthcare systems in-country" - Dr Maurine Murtagh

For instance, the goal of many of the EID studies has been to link HIV-infected infants to care. But there was more than one study at AIDS 2012 describing high rates of loss to follow-up among children who have started ART. [In one study from Lilongwe, Malawi](#), the only risk factors significantly associated with loss to follow-up among children on ART were wasting and being under the age of two (precisely the population most at risk.)

Making the best of DBS for EID in the meantime

But point-of-care tests still have regulatory hurdles to clear, and it could take more than five years for tests to become available, even after there is a prototype, said Dr Murtagh.

So, in the meantime, can anything be done to make better use of the tools we've got?

Dr Abubakar hasn't given up trying to improve EID in his setting. Working with CHAI, MSH will be piloting the deployment of SMS printers, small portable devices that can receive and print the DBS results from the regional labs to the EID site, printing them out just after the sender enters them, which would take care of the time accrued waiting for the post to arrive. (Another obviously expensive option is an electronic system, like South Africa's National Health Laboratory Service has established.)

MSH ProAct is instead working with the Nigerian Postal Services on the transport of DBS samples from EID sites to the Regional lab using the Express Mail Service (EMS). They are also providing more training and re-training of service providers on DBS sample collection and dispatch. During one symposium, Dr Mbori-Ngacha of UNICEF highlighted several examples of best practices for improving retention and rates of early infant diagnosis:

- In Uganda community volunteers accompanying children to clinics reduced loss to follow-up by 69%;
- Providing transport vouchers in Uganda increased in-facility deliveries from 200 to 500 a month;
- In South Africa using patient advocates within the service improved retention from 81.1% to 91.5%;
- In Tanzania quality improvement reduced loss to follow-up from 22% to 14%;
- In Zambia training providers reduced loss to follow-up from 10.7 to 7.1%;
- In Malawi cell phones increased the rate of early infant diagnosis from 30% to 80%.

Several studies emphasise that community or peer health workers can help make sure that results are received, and linkages to care effective. Delivery of EID results went up to 99% in Bulawayo, with the assistance of peer supporters from Mothers2Mothers.

Track and act

Dr Essajee also highlighted the need for each actor in the referral chain 'to get their act together, and for each care provider to do their bit: make sure the paper work is correct, that proper data has been recorded and reported and that they collect the proper contact data for mother-infant pairs that are tested by EID. While waiting for results, the health services could reach out to provide support and follow-up to prepare mothers for the child's result. They should use triplicate forms to track which babies make it to referral (one copy to the clinic, one copy to the lab, one copy to the referral clinic). Facilities should have procedures in place to provide follow-up and track mother-infant pairs who do not return for their results. Healthcare providers or counsellors should work with the patients before they are referred to find some sort of mechanism that works as an incentive to complete the referral. "Allay their fears about infant treatment," he said, "explain that it is lifesaving, it is free, it is simple and most children tolerate it very well."

ART sites also need to do more to accommodate infants with HIV and "also make it easier for the infant to start ART when they get to the clinic," he said. They should be ready when the child arrives and have paediatric ARV formulations already in stock.

However, both Dr Essajee and Dr Abubakar are looking ahead to point-of-care tests, which one hopes, will resolve many of these issues.

"These initiatives are concrete steps being taken by the project and cannot substitute for a point of service technology which is the ultimate goal, but in the meantime, we have to try to shorten turnaround time. Fortunately, we do have hope now that this will be addressed soon with a point of service technology for early infant diagnosis expected by 2013," Dr Abubakar told HATIP.

References

- [1] Diener LC et al. *Performance of the integrated management of childhood illness algorithm for diagnosis of HIV-1 infection among African infants*. AIDS 26(15):1935-41, 2012.
- [2] Goga A et al. *Impact of the national prevention of mother to child transmission (PMTCT) program on mother-to-child transmission of HIV (MTCT), South Africa, 2010*. 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract MOAC0206, Rome, 2011.
- [3] Rollins et al. *Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening*. AIDS 21(10): 1341-7, 2012.
- [4] Horwood C et al. *Elimination of paediatric HIV in KwaZulu-Natal, South Africa: large-scale assessment of interventions for the prevention of mother-to-child transmission*. Bulletin of the World Health Organization 90:168-175, 2012.
- [5] Hussain A et al. *Pregnant women's access to PMTCT and ART services in South Africa and implications for universal antiretroviral treatment*. PLoS ONE 6(12): e27907, 2011.
- [6] Nwuba CO et al. *A laboratory-based approach to reduce loss to follow-up of HIV-positive clients*. 19th International AIDS Conference, Washington, abstract WEAE0202, 2012.
- [7] GNP+/WAC LTA Report. In press.
- [8] Dow DE et al. *PMTCT performance among HIV-positive infants in Tanzania*. 19th International AIDS Conference, Washington, abstract WEPE198, 2012.
- [9] Dadabhai S et al. *Child health outcomes in Blantyre, Malawi: 20-years of data from multiple longitudinal HIV cohorts*. 19th International AIDS Conference, Washington, abstract MOPE131, 2012.
- [10] Nyathi M et al. *Starting ART early: is there any progress? Experiences and lessons from Zimbabwe's largest child cohort*. 19th International AIDS Conference, Washington, abstract MOPE195, 2012.
- [11] Atukunda R et al. *Factors associated with mortality among paediatric patients on antiretroviral therapy in 18 AIDSRelief sites in Uganda: a cause for concern?* 19th International AIDS Conference, Washington, abstract MOPE039, 2012.
- [12] Zanon BC et al. *Risk factors associated with increased mortality among HIV infected children initiating antiretroviral therapy (ART) in South Africa*. PLoS ONE 6(7): e22706, 2011.
- [13] Rahma NE et al. *Mortality among HIV-positive children after receiving highly active antiretroviral therapy at OMACU Center, Khartoum, Sudan*. 19th International AIDS Conference, Washington, abstract TUPE038, 2012.
- [14] Vermund SH et al. *Poor clinical outcomes for HIV infected children on antiretroviral therapy in rural Mozambique: need for quality improvement and continuing program/community development in PEPFAR*. 19th International AIDS Conference, Washington, abstract MOPE068, 2012.
- [15] Violari A et al. *Early antiretroviral therapy and mortality among HIV-infected infants*. N Engl J Med.359(21):2233-2244, 2008.
- [16] Ibid.
- [17] Nyathi M et al. *Starting ART early: is there any progress? Experiences and lessons from Zimbabwe's largest child cohort*. 19th International AIDS Conference, Washington, abstract MOPE195, 2012.
- [18] Mushavi A et al. *Retention of children in HIV treatment and care programmes*. 19th International AIDS Conference, Washington, 2012.
- [19] Abubakar A et al. *Towards an HIV-free generation: prospects and challenges of determining the outcomes of prevention of mother-to-child transmission of HIV program in hospitals in Kwara State, north central Nigeria*. 19th International AIDS Conference, Washington, abstract WEPE188, 2012.
- [20] Dube Q et al. *Implementing early infant diagnosis of HIV infection at the primary care level: experiences and challenges in Malawi*. Bulletin of the World Health Organization 90:699-704, 2012.
- [21] Schouten EJ et al. *More HIV-positive infants and mothers identified through HIV testing in immunization clinics*. 19th International AIDS Conference, Washington, abstract THAC0102, 2012.
- [22] Landes M et al. *Mortality and health outcomes of HIV-exposed and unexposed children in a PMTCT cohort in Malawi*. 19th International AIDS Conference, Washington, abstract WEPE161, 2012.
- [23] van Lettow M et al. *Uptake and outcomes of a prevention-of mother-to-child transmission (PMTCT) program in Zomba district, Malawi*. BMC Public Health 11:426, 2011.
- [24] McCollum ED et al. *Clinical diagnosis versus expedited virologic testing for HIV infection in hospitalized Malawian infants: a randomized controlled proof-of-concept trial of point-of-care infant testing*. 19th International AIDS Conference, Washington, abstract LBPE13, 2012.
- [25] Sherman G. *Recognizing risk in HIV-exposed and -infected infants and children. Diagnosing HIV infection in infants: are we there yet?* 19th Conference on Retroviruses and Opportunistic Infections, Seattle, 2012.
- [26] Chamie G et al. *Leveraging rapid community-based HIV testing campaigns for non-communicable diseases in rural Uganda*. PLoS One 7(8): e43400, 2012.
- [27] Jani IV et al. *Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study*. The Lancet 378 (9802): 1572-9, 2011.
- [28] Bergeron M et al. *Performance of the PointCare NOW system for CD4 counting in HIV patients based on five independent evaluations*. PLoS One 7(8): e41166, 2012.
- [29] Mahomva AI et al. *An innovative, rapid national scale-up of effective PMTCT services in a resource-limited setting to facilitate virtual elimination of new pediatric HIV infections by 2015: A Zimbabwe experience*. 19th International AIDS Conference, Washington, abstract WEPE737, 2012.
- [30] Muchedzi et al. *Evaluating the effect of the use of point-of-care CD4 machines on access to eligibility screening and ART initiation for HIV-positive pregnant women in Zimbabwe: towards elimination of new paediatric HIV*

infection by 2015. 19th International AIDS Conference, Washington, abstract

TUPDE0204, 2012.

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