

Mid-term evaluation report

NACCAP programme second call

'Developing an Affordable HIV drug Resistance Test for Africa: the ART-A programme'



The Hague, December 2009

Foreword

In 2004, the Dutch Ministry of Foreign Affairs (DGIS) made available € 20 M to contribute to EDCTP through the Netherland African Partnership for Capacity Development and Clinical Interventions against Poverty related Diseases (NACCAP) programme. The general aim of NACCAP is to support investment in strengthened research and development capacity of multiple locally owned and controlled health research centres in sub-Saharan Africa, capable of clinical testing of new interventions against poverty related diseases and contributing to the EDCTP objectives. A partnership programme ART-A was awarded in the second NACCAP call that aimed at strengthening of R&D capacity of African owned (pharmaceutical or biotechnological) R&D institutes by technology transfer between African and European private and public institutes.

In October 2007, a partnership programme of the second NACCAP call, ART-A, started, with funding for an initial one and a half year. Funding could continue up to 2010 if the results of a mid-term review (MTR) to assess if the partnership programme is indeed contributing to the objectives of NACCAP were favourable. In September 2009, a MTR of ART-A was performed by NACCAP and the results of the review are presented in this report.

The MTR-committee was composed of one member with expertise in the field of capacity strengthening of African research institutes (Dr Andrew Kitua), one member of the NACCAP programme committee with expertise in the field of project management in health research and private sector involvement (Dr Opokua Ofori-Anyinam); one member of the NACCAP programme committee with expertise on translating research into health policy (Dr Irene Agyepong) as chair; and two members of the NACCAP secretariat (Dr Judith de Kroon & Dr Eva Rijkers) for administrative support. A written mid-term review report of ART-A was assessed, and a site visit was paid to South Africa.

The MTR committee observed that ART-A is scientifically sound, clearly focused, and well on schedule. The consortium partners have created an open, enthusiastic and equal partnership, generating rapid scientific progress. The consortium is well embedded in the national research for health policy agenda-setting organisations in South Africa and the partnership has established links with research for public health and IPR systems pro-actively. Technology transfer within the consortium (from private sector to public sector partners) is well on track. However, the technology transfer and capacity building aspect of the programme from the ART-A consortium to the regional Centres of Excellence and the other partner clinics has not yet received as much attention and consideration as the scientific aspect. No coherent plan aimed at the sustainability of capacity strengthening activities and phased implementation of the algorithm at the Centres of Excellence and other affiliates sites exists and this should be developed as soon as possible.

The MTR committee concluded that none of the challenges are insurmountable such that the programme needs to be terminated. The challenges do however need to be addressed to make sure that NACCAP objectives are fully achieved with continued funding. The MTR committee therefore recommends that the ART-A programme be funded up to and including 2010 but on the condition that the recommended suggestions for modifications are implemented.

Last, but not least, the MTR committee wishes to express its appreciation to the ART-A team for their hospitality, welcome, cooperation and open discussions and interactions with the committee. Without the efforts they put into facilitating the MTR, it would not have been possible to achieve so much in such a short time. The MTR committee commends the team for the work already done, and looks forward to seeing continuing strong partnership within the ART-A consortium and sustainable technology transfer and capacity strengthening.

Yours sincerely,

Irene Agyepong,
Chair of the MTR committee

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PART A: GENERAL INTRODUCTION

1. Background information: EDCTP

In 2002, the Member States (MS) of the European Union, Norway and the Developing Countries (DCs), particularly sub-Saharan Africa, came together to establish a sustained partnership to reinforce research into the development of new clinical interventions to fight HIV/AIDS, malaria and tuberculosis. This resulted in 2004 in the European & Developing Countries Clinical Trial Partnership (EDCTP), the first programme financed by the instrument of Article 169 of the 6th Framework Programme of the European Commission. The mission of EDCTP is to accelerate the development of new clinical interventions to fight HIV/AIDS, malaria and tuberculosis in, particularly, sub-Saharan Africa and to improve generally the quality of research in relation to these diseases. The main objective of EDCTP is to contribute to the integration of European research in these fields. Within its mission, EDCTP aims at the establishment of a sustained research partnership between Europe and Africa in the fight against the three diseases.

In 2004, the Dutch Ministry of Foreign Affairs (DGIS) made available € 20 M to contribute to EDCTP. Because at that time the implementation strategy of EDCTP was not clear, the Dutch ministry decided to contribute to EDCTP through the NACCAP programme; the Netherlands-African partnership on Capacity strengthening and Clinical trials against Poverty-related diseases; a research and capacity strengthening programme managed by NWO/WOTRO.

2. Background information: NACCAP

The general aim of NACCAP is to provide an impulse to the investment in, and development of, **African owned** and controlled health research centres aimed at and **capable of clinical testing** of new interventions against poverty related diseases. As a result, the position and contribution of African institutes in EDCTP will be strengthened, supporting **partnerships in joint R&D** activities to fight poverty related diseases in Africa. NACCAP aims at **transferring responsibilities** for sustained developments to the supported African centres: for this, the centres (2-5) strengthened should become **part of an African Network of R&D centres** capable of **collaborating with EDCTP** in clinical trials.

In 2004 EDCTP took off as a research-funding organisation that awarded separate, small grants, focussing on collaborative EU-African research rather than on capacity strengthening¹. However, the NACCAP Steering Committee (SC) thought this was not the optimal way to achieve the objectives and therefore decided to announce a call for proposals on its own, with the aim to fund African-Dutch partnerships consisting of integrated multidisciplinary R&D projects which contribute to institutional capacity development of African research centres. In addition, because NACCAP aims at strengthening centres that can collaborate with EDCTP in clinical trials, preferably the awarded partnerships included researchers from other European countries (N-N networking).

NACCAP's second call was focused on translational research, in which science is translated into clinical application by partnerships between private and academic institutes in order to enhance the development of new products. In addition, technology transfer on small scale production of clinical products (against HIV/aids, malaria and tuberculosis) according to international accepted standards is financed. In doing so, sustainable strengthening of African R&D capacity e.g. by technology transfer of partnerships between private (industrial) and public (academic) partners is a prerequisite.

3. Goal of the midterm review

As a result of this second call, one partnership programme (ART-A) was selected for funding for 1,5 year and funding will continue up to September 2010 on the condition that the results of a mid-term review are favourable.

¹ During the course of 2005 the interpretation of article 169 was further developed and in 2006 EDCTP changed its strategy into a strategy more in line with the NACCAP approach.

The ART-A programme started on 1 October 2007² and was reviewed in September 2009.

The **goal** of the mid-term review is to assess if the partnership programme is indeed contributing to the objectives of NACCAP and specifically to the objective of the second NACCAP call, i.e:

- to strengthen R&D capacity of African owned (pharmaceutical or biotechnological) R&D institutes by technology transfer between African and European private and public institutes.

Since the partnership proposal was selected on the basis of the quality of capacity strengthening, scientific quality and governance (including equality of the partnership and African ownership), progress with regard to these aspects are specifically being reviewed.

4. Methodology of the Mid Term Review

For the mid term review, a specific Mid Term Review (MTR) committee was composed, consisting of two experts, one in the field of project management in health research and private sector involvement (Dr Ofori-Anyinam) and one in the field of capacity strengthening of African research institutes (Dr Kitua). The MTR committee is chaired by an expert on translating research into health policy (Prof. Agyepong), and assisted by the NACCAP secretariat.

Composition of the MTR committee:

Chair: Prof. Irene Agyepong, NACCAP Programme Committee, Director Ghana Health Service Greater Accra Regional Health Directorate, Accra, Ghana and holder of the Prince Claus Chair in Development and Equity, 2008 – 2010, Utrecht University;

Members: Dr Opokua Ofori-Anyinam, Senior Manager, GlaxoSmithKline Biologicals, Belgium;
Dr Andrew Kitua, Leader of the Antimalarial policy and access unit of the Special Programme for Research and Training in Tropical Diseases (TDR), WHO, Geneva;

Secretariat: Dr Judith de Kroon & Dr Eva Rijkers, NACCAP secretariat, NWO/WOTRO

Tasks of the MTR committee:

The tasks of the MTR committee are:

Prepare MTR:

- 1 Take note of the background documents:
 - original NACCAP background document;
 - second call text;
 - the original partnership proposal;
 - site assessment (before start of the partnership programme) report;
 - annual report of the partnership programme 2008;
 - overview of the NACCAP comments on the annual report;
 - MTR form, including testable goals;
 - preliminary SWOT (by ART-A).
- 2 If necessary, adjust testable goals that will also serve as the programme outlines for presentations to be held by partnership;
- 3 Ask programme co-ordinators to complete the MTR form;
- 4 Formulate specific review questions;
- 5 Propose a list of participants / stakeholders whom the MTR committee would like to interview during the site-visit;

Visit the partnership programmes:

- 6 Take note of the MTR testable goals form, completed by the co-ordinators of the partnership programmes and formulate review questions;
- 7 Visit the partnership programme site in Africa and meet with the main African participants of the partnership programme. For this a meeting will be organised by the partnership;

² As programme start date 1 October 2007 was taken, because this was the starting date of the first ART-A employee (as indicated on the Personnel Information Form (PIF) sent to WOTRO).

- 8 Interview individuals (programme participants, other stakeholders) to answer specific questions of the committee;

Contribute to the report:

- 9 Write a report and formulate conclusions, including recommendations for improvements/ future activities;
- 10 Discuss the report with the coordinators of the partnership programmes for comments and if relevant, adjust the report accordingly;
- 11 Present the (adjusted) report to the NACCAP Programme Committee.

Based on the report, the NACCAP Programme Committee will formulate recommendations with regard to improvements to be made and continuation of funding to the NACCAP Steering Committee who will decide.

5. Contents of the report

The reportage of the MTR of ART-A (Part B) is included in this report and is composed as follows:

Chapter 1 of the reportage includes a short summary of the conclusions and recommendations of the MTR committee. In **chapter 2**, a short description of the partnership programme and the environment in which it operates is described, followed by **chapter 3** that provides the results of the site MTR including the progress of the partnership programme. For this, the testable goals are taken as a lead. Progress with regard to each testable goal is followed by a preliminary conclusion of the MTR committee and the MTR committee's recommendations. **Chapter 4** includes some bottlenecks for the future identified by the partnership programme. Furthermore, the annexes provide some detailed information on the partnership site visit programme (annex 1), ART-A SWOT analysis (annex 2) and abbreviations used (annex 3).

PART B: ART-A

Reportage of the MTR of the 'Developing an Affordable HIV drug Resistance Test for Africa: the ART-A programme'

1. Summary

ART-A is a research, technology transfer and capacity strengthening programme focussing on developing and implementing an affordable HIVDR diagnostic test for Africa. Within ART-A, six consortium partners from South Africa, Belgium, Luxemburg and the Netherlands work together to develop an affordable HIV drug resistance test that can be implemented throughout Africa. These six consortium partners are:

- The Center for Poverty-related Communicable Diseases (CPCD) through the PharmAccess Foundation, Amsterdam, the Netherlands;
- Dept. of Virology, University Medical Centre Utrecht (UMCU), Utrecht, the Netherlands;
- CRP Santé, Luxemburg, Luxemburg;
- Virco, Mechelen, Belgium;
- Dept. of Molecular Medicine and Haematology, Witwatersrand University (Wits), Johannesburg, South Africa;
- Contract Laboratory Services (CLS), Johannesburg, South Africa.

Scientifically, the ART-A programme focuses on the development of an affordable HIV drug resistance test. This includes the development of an easy to use device to transport samples to reference labs (dried blot spots, DBS), development of a sequencing protocol, as well as the development and testing of an algorithm capable of translating genotypic data into a phenotypic analysis. The development of these tools is performed by the six ART-A consortium partners in a joint effort. These different tools will then be implemented at several affiliated African clinics, starting with reference laboratories or African regional Centres of Excellence.

For this, the ART-A programme is composed of five projects, each coordinated by one of the consortium partners:

1. Development of a convenient sample collection device and extraction protocol
2. Development of affordable genotypic applications
3. Implementation and optimization of genotypic interpretation systems
4. Technology transfer and Training Work Package
5. Dissemination and communication

Throughout the programme, technology transfer from the private sector consortium partners to the public sector consortium partners is included. Projects 4 and 5 specifically aim at transfer of technology to and building capacity at several regional Centres of Excellence (CoE; starting with Wits itself and JCRC in Uganda) and a number of other partner clinics throughout Africa. At these CoE and other partner clinics, samples are collected for the development and validation of the algorithm. As mentioned in the original ART-A application, these partner clinics will participate in sample collection for evaluation by consortium partners and benefit from training programmes on GCLP and HIVDR testing issues, capacity building, and implementation of the algorithm.

Scientifically, the ART-A programme is sound, clearly focused, and well on schedule, despite the late start of the two PhD students³. The consortium partners have created an open, enthusiastic and equal

³ ART-A responded to this comment in the MTR report as follows: "After reception of the grant approval letter in November 2007, numerous attempts have been made to organize a kick off meeting with the ART-A consortium in December of that year. Due to other obligations of the ART-A consortium partners and the South African holiday period, the first option for the kick-off meeting was directly after the CROI in February 2008. Immediately after this meeting, the advertisement and recruitment of PhD students was started. The advertisement, interviewing of candidates, selection and recruitment process took 3 months; the 2 recruited

partnership, generating rapid scientific progress. The consortium is well embedded in the national research for health policy agenda-setting organisations in South Africa and the partnership has established links with research for public health and IPR systems pro-actively. Technology transfer within the consortium (from private sector to public sector partners) is well on track. A concern for the scientific projects is that the time remaining within ART-A for the PhD students to finish their theses is insufficient.

However, the technology transfer and capacity building aspect of the programme from the ART-A consortium to the regional Centres of Excellence and the other partner clinics has not yet received as much attention and consideration as the scientific aspect. For technology transfer and capacity development to be sustainable, it is crucial that a stepwise plan to build capacity of the affiliated partners in a sustainable way is discussed thoroughly and equally amongst all consortium and affiliated partners at the earliest opportunity. Especially the role the reference labs (regional Centres of Excellence) could play in assisting capacity strengthening and technology transfer to the other partner clinics should be discussed as soon as possible. In addition, commitment of policy makers and other stakeholders in these countries is crucial for sustainable capacity strengthening and technology transfer, as well as implementation and use of the algorithm that is being developed. Therefore, this commitment should actively be sought as soon as possible.

In conclusion, the MTR committee thinks that although the ART-A programme is well on track scientifically, it should now quickly turn its focus to sustainable technology transfer and capacity strengthening. In order to do so, the MTR committee recommends ART-A to:

1. Continue the efficient and successful scientific path chosen and maintain the effective private to public technology transfer activities. In addition, maintain the open, equal and committed partnership;
2. Develop a coherent plan aimed at improving the sustainability of capacity building activities within ART-A, including a plan to ensure use of the new knowledge and technologies and strategies to retain trained staff;
3. Develop a well thought-through stepwise implementation plan, starting with sustainable capacity strengthening, technology transfer and implementation of the algorithm at the regional Centres of Excellence (currently identified: Wits and JCRC, potential candidate: ICRH in Mombasa, Kenya). These Centres of Excellence can then assist in implementing the algorithm at other partner clinics and a plan for this should be developed as well;
4. Develop a clear communication and dissemination plan, including a forum for feedback from the Centres of Excellence and other partner sites;
5. Involve all stakeholders (thus, the consortium partners, the regional reference labs/ Centres of Excellence, the other partner clinics, and local policy makers) in the development of all three above-mentioned plans and include several possibilities for the associated partners to share their views on all aspects of the programme. This will increase the ownership of the Centres of Excellence and the other partner clinics;
6. More strongly involve the Centres of Excellence and other partner sites in the ART-A governance structure, for example by creating a capacity strengthening/ technology transfer advisory board composed of representatives from the Centres of Excellence and other partner clinics;
7. Draft a plan to ensure that the PhD students can successfully finish their PhD theses after the ART-A subsidy has ended.

PhD students started respectively on 1st July and 1st August 2008, as soon as they had completed their previous duties.”.

2. The partnership programme

Description of the partnership programme

ART-A is a research, technology transfer and capacity strengthening programme focussing on developing and implementing an affordable HIV drug resistance (DR) test for Africa. Within ART-A, six consortium partners from South Africa, Belgium, Luxemburg and the Netherlands work together to develop an affordable HIV drug resistance test for Africa. These six consortium partners are:

- Center for Poverty-related Communicable Diseases (CPCD) through the PharmAccess Foundation, Amsterdam, the Netherlands;
- Dept. of Virology, University Medical Centre Utrecht (UMCU), Utrecht, the Netherlands;
- CRP Santé, Luxemburg, Luxemburg;
- Virco, Mechelen, Belgium;
- Dept. of Molecular Medicine and Haematology, Witwatersrand University (Wits), Johannesburg, South Africa;
- Contract Laboratory Services (CLS), Johannesburg, South Africa.

Within ART-A, the consortium partners combine their knowledge and expertise to develop an affordable and practical solution for HIVDR determination in Africa. In order to achieve this goal, the ART-A programme is composed of the following three research and two capacity building projects:

1. Development of a convenient sample collection device and extraction protocol to facilitate HIV drug resistance testing in resource limited settings
2. Development of affordable genotypic applications
3. Implementation and optimization of genotypic interpretation systems
4. Technology transfer and Training Work Package
5. Dissemination and Communication

Projects 1, 2 and 3 are research projects strongly related to each other, whereas projects 4 and 5 aim at technology transfer and dissemination to the African affiliated partners. Each project is coordinated by one of the consortium partners.

In project 1, the consortium is testing a sample collection method and extraction protocol which is based on dried blood spots (DBS), in order to make it compatible with African field conditions. In project 2, the consortium partners are developing an affordable subtype independent methodology for HIVDR sequencing compatible with the DBS sample collection method. In addition, the consortium is developing a genotypic interpretation system based on the VircoType HIVDR interpretation software for African HIV-1 subtypes in project 3. The consortium aims for this software to be web-based and freely available to interested clinics in Africa. Different levels of the protocol are being developed so that African partner clinics with different levels of available infrastructure can implement this protocol. Training, dissemination and technology transfer from the consortium partners to these partner clinics is done through projects 4 and 5.

The ART-A partnership aims to serve two goals by setting up resistance testing: public health and patient care. Resistance tests performed throughout Africa will be an important surveillance mechanism to monitor HIV drug resistance in Africa. In addition, individual patient care will be improved by the availability of affordable resistance tests, as a timely, more informed decision on treatment can be made (provided results of the new DR test will be available within approximately two weeks).

The ART-A programme is, through PharmAccess and to a lesser extent also via Wits and UMCU, linked to another large programme on HIV drug resistance in Africa: PASER (PharmAccess African Studies to Evaluate Resistance). PASER is funded by the Netherlands Ministry of Foreign Affairs and aims to build capacity on the monitoring and surveillance of HIVDR in Africa. Secondary aims of PASER are to evaluate the success of antiretroviral programmes to prevent or minimize HIVDR in selected geographical settings, to identify specific HIVDR mutations and mutational patterns, and to create an international observational database.

Because most of the sites currently affiliated with ART-A were already members of the PASER network, PASER provides ART-A with the clinical, laboratory, logistical and managerial framework for embedding the novel HIVDR test into the African setting. For example, research samples (dried blood spots) are collected for development of the algorithm at partner clinical sites. In a later stage, samples collected at these partner clinics will be used for validation of the algorithm. The original ART-A application mentions that these partner clinics will participate in sample collection for evaluation by consortium partners and benefit from training programmes on GCLP and HIVDR testing issues, capacity building, and implementation of the algorithm. The clinics affiliated with ART-A (as presented by ART-A during the MTR site visit) are:

- Themba Luthu Clinic, Johannesburg, South Africa
- Muelmed Hospital, Pretoria, South Africa
- Lusaka Trust Hospital, Lusaka, Zambia
- Kara Clinic, Lusaka, Zambia
- Coptic Hospital, Hope Centre, Lusaka, Zambia
- International Centre for Reproductive Health/ Coast Province General Hospital, Mombasa, Kenya
- Joint Clinical Research Centre, Kampala, Uganda;
- Lagos University Teaching Hospital, Lagos, Nigeria;
- Newlands Clinic, Harare, Zimbabwe;
- The Mater Hospital, Nairobi, Kenya.



Sign outside the Muelmed Clinic, Pretoria

Not all these clinics will be able to implement the full algorithm developed within the ART-A programme. Within ART-A, the definition system of PharmAccess is used to determine the level of the different clinics. For example, a tertiary teaching hospital able to provide all specialised medical procedures is defined as a level A clinic, whereas a nurse driven health shop is defined as level E clinic. According to the level of the different partner clinics per this definition system, the full algorithm or one of two simpler versions will be implemented at the partner clinics. Currently, only two level A clinics (reference laboratories) in Africa have been identified to perform the full resistance algorithm: Wits University and JCRC in Uganda. The ICRH in Mombasa is a candidate reference clinic expected to be able to also implement the full resistance algorithm. In lower category clinics, DBS can be taken and sent to the reference lab where viral load tests will be performed, if needed followed by a resistance test. The results from these tests can then be returned to the clinic.

Environment

Organisational environment

Within ART-A, six consortium partners have joined forces to develop and implement an affordable HIVDR test for Africa. At the very start of the partnership programme, these six consortium partners have signed a consortium agreement, arranging issues such as obligations of each partner, programme steering committee and IPR and access and publication issues.

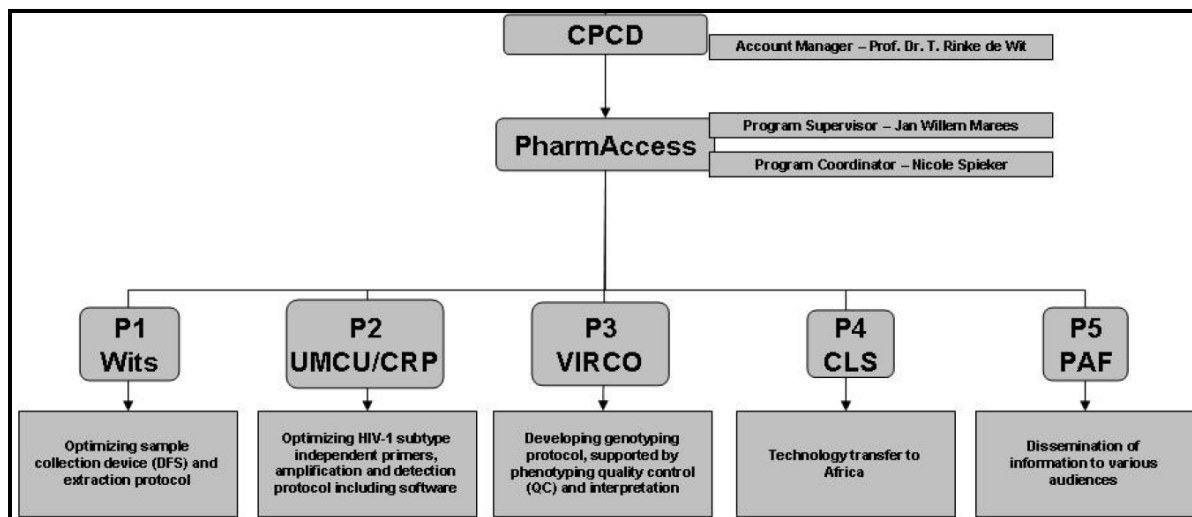


Figure 1. Organisation of the ART-A programme

PharmAccess is a not-for-profit organisation dedicated to expanding access to sustainable HIV/ AIDS care and treatment in resource limited settings, especially in Africa. The Center for Poverty-related Communicable Diseases of the Amsterdam Medical Center (CPCD) is the coordinating scientific institute of ART-A and subcontracts PharmAccess for programme implementation. PharmAccess coordinates project 5, as well as the ART-A programme as a whole, and provides a link to a number of clinics in (currently) 6 African countries through its PASER programme.

Project 1 of ART-A is coordinated by the Department of Molecular Medicine and Haematology of Witwatersrand University. This department is leading the development of affordable disease surveillance and diagnostics in South Africa. It hosts the ART-A PhD student performing project 1 and is currently one of two regional molecular reference labs in Africa.

The Department of Virology at the UMCU hosts and coordinates PhD project 2. Within ART-A project 2, candidate subtype independent amplification primer sets (previously developed by the UMCU) are being tested.

CRP-Santé's retrovirology lab provides specific knowledge on different dried fluid spot applications as well as software design for manipulation of genetic sequences. CRP is also involved in the coordination of project 2, as it coordinates project 2b.

Virco is based in Mechelen and is a private partner in the consortium, providing a HIV-1 genotyping system that is based on a database of matching genotypes and phenotypes and can thus provide a phenotypic interpretation of a genotype. Virco provides their genotyping and phenotyping algorithms in return for access to data to improve their predictive algorithms. Within the ART-A programme, Virco hosts and coordinates project 3 and is a strong technical supporter of the PhD programmes: the PhD students receive training at Virco.

CLS (Contract Laboratory Services) is a private partner offering diagnostic lab services for clinical trials and research studies. CLS has ample expertise in training and capacity building in clinical lab settings and aims to be the training hub for Africa for this. Within ART-A, CLS coordinates project 4 and is responsible for rolling out technology and education received from Virco to the African partner clinics, as well as other project education and technology transfer. The contribution of CLS to the ART-A programme consists of in kind contributions by arranging the workshops.

The ART-A consortium is well embedded in the South African national research for health policy agenda setting organizations. For example, within South Africa, strong connections between ART-A and the National Health Laboratory Service (NHLS) exist. NHLS is the obligatory laboratory provider for the public health system. It is part of the national department of Health and is a fee for service organisation providing lab services. In addition, NHLS has two other mandates: education of all pathologists in South Africa (through direct contacts with eight health faculties) and research. NHLS has a clear research strategy and only takes on donor-funded projects that fit into that strategy. An important focus of the

NHLS is affordability of new interventions and all research proposals should include a cost-benefit analysis from the start. NHLS is strongly committed to capacity strengthening of South African research institutes, in terms of leadership, but also for example administration. Furthermore, ART-A (through Wits) has contacts with the Southern African Clinicians Society, which is interested in ART-A in view of the possible link between researching resistance with clinical data, especially for policy making. The School of Pathology of Wits University & NHLS is committed to ART-A as it fits very well within the strategy of the School of Pathology.



*The ART-A partnership contains strong South African partners:
Strict security measures at CLS*

3. Progress

• Testable goals

In order to measure progress, several testable goals and related review questions were formulated by the MTR committee. In summary, the testable goals are:

- Relevance (with regard to individual, institutional and environmental capacity strengthening, and with regard to science);
- Governance (contributing to equal partnership and/or African ownership and embedding while safeguarding transparency and accountability);
- Efficiency (is progress on schedule);
- Effectiveness

In addition, some challenges for the future of ART-A were identified.

• Results

1. Relevance

a) contributing to strengthened research & development capacity of a locally-owned health research centre in Sub-Saharan Africa.

Capacity strengthening and technology transfer within the ART-A programme can be divided into three phases:

1. Technology transfer within the consortium, from private sector partners to public sector partners;
2. Capacity strengthening of and technology transfer from the consortium partners to African Centres of Excellence;
3. Capacity strengthening and technology transfer from the African Centres of Excellence to the other African partner clinics.

The capacity strengthening and technology transfer activities of the ART-A consortium partners (phase 1) are integrated in all five ART-A projects. For capacity strengthening of partner sites (trainings as well as technology transfer; phase 2 and 3), ART-A developed a separate project: Technology transfer and Training Work Package (project 4, coordinated by CLS).

Individual level

Individuals from the consortium partners (for example the two South African PhD students) receive training through workshops and courses, as well as on-the-job training. The two ART-A PhD students will defend their thesis both at Wits and in Amsterdam. In addition to the 2 PhD students, 1 project manager and 4 technical staff of the ART-A programme have acquired new technical skills up to now.

Within project 4, a workshop was held in Kenya in November 2008 where individuals from the African partner clinics (4 scientists, 20 doctors and 18 counsellors) attended a workshop on principles of HIV drug resistance, affordable HIV diagnostics, and clinical interpretation and use of HIV drug resistance results. In addition, 2 scientists, 1 counsellor and 12 technicians attended workshops on molecular GCLP, principles of HIV drug resistance, and introduction to HIV drug resistance testing. These trainings were not closed by an exam, but by a post-course questionnaire. It is unclear to the MTR committee whether the participants played an active role during these workshops or whether they merely received information⁴. In addition, besides upfront selection of training participants, ART-A does not seem to have a coherent strategy in place to ensure that these trainees use the newly acquired knowledge and skills: no incentives are in place for the trainees to actually use this knowledge. Therefore, it is unclear to the MTR committee whether individual capacity has been built in a sustainable manner.

⁴ ART-A responded to this comment in this MTR report as follows: "In general, the participants of this workshop played an active role, because of its interactive nature. The focus of this first training was on information dissemination to those who were considered future candidates for ART-A capacity building. It was too early to transfer newly acquired ART-A knowledge, simply because this knowledge did not yet exist; the lab work of ART-A had just started. Transfer of new ART-A skills and technologies was planned for a next workshop in November 2009."

Furthermore, preparations are ongoing for a workshop scheduled to be held in Lusaka, Zambia, in November 2009. After the first workshop in Kenya, the ART-A consortium realised that senior lab technicians required a different training level than junior lab technicians. Therefore, during the Lusaka workshop, different levels of trainings will be offered. Selection of participants for the workshops is based on consultation of managers of involved labs and on information from WHO on which labs would fit in the ART-A programme. The ART-A consortium aims to train 20 doctors in resistance interpretation skills and adherence and 20 junior technicians in GCLP at this Lusaka workshop.

However, different partners of the ART-A consortium appear to have different training aims for the participants in this workshop. For example, during the MTR site visit it was unclear whether the senior lab technicians will be trained in molecular tools for HIV diagnostics, or lab and project management (aimed at gaining understanding of what it takes to set up a lab facility at a higher level), or both⁵.

Institutional level

ART-A aims to strengthen the capacity of the African consortium partners Wits and CLS through transfer of technologies from the European partners. Currently, VircoNET software transferred from Virco is being used at Wits and several technologies transferred from European partners are used by researchers at African institutes. Technology transferred is embedded within the African consortium partner institutions via SOPs, Work Instructions and Manuals. Through these activities, Wits is expanding its regional HIV drug resistance hub role.

*Table 1: Level of Partnership programme **African consortium partners** at this moment: level at the review moment*

Level	1	2	3	4
Components	<i>Epidemiological relevant population and interested investigators</i>	<i>Identified cohort and follow-up capability</i>	<i>Sites with some clinical trial capacity (indicate phase)</i>	<i>Fully capable site for phase I-III trials</i>
1. Investigators	Lacks GCP	GCP exposure	GCP qualified with limited experience	GCP qualified with experience
2. Subjects	Target population identified	Demonstrated ability to follow-up. Community involvement	Demonstrated ability to follow-up. Community involvement formalise	Demonstrated ability to follow-up. Community development Programme
3. Ethics	IRB not yet established	IRB National ethics Committee exists	IRB National guidelines for clinical trials exist	IRB National guidelines for clinical trials exist
4. Laboratories	Access to laboratory facilities	GLP exposure	GLP qualified with limited experience	GLP qualified with experience
5. Clinical facilities	Ability to measure clinical outcomes	Access to facilities with staff	Adequate facilities and qualified staff	Excellent facilities with qualified staff
6. Data management	Data collection field staff	Some computer infrastructure and basic data-processing skills	Sufficient computer hardware and software Experienced data-processing staff.	Biostatistics, sufficient computer hardware and software. Experienced data-processing staff
7. Sample repository	absent	Some, but temporary/ sporadic	Part of laboratory	Available (cold) chain
8. IPR skills	absent	External qualified advisor available	Some internal qualified skills available	Experienced qualified personnel available within centre
9. Administration	Basic administrative capability	Basic administrative Capability	Accounting and administrative	Well established and audited accounting

⁵ ART-A responded to this comment as follows: "They will be trained in molecular tools for HIV.".

			systems available	and admin systems
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In addition, the ART-A partnership aims to contribute to capacity strengthening of African regional Centres of Excellence (reference laboratories) by transfer of the new HIVDR technology (when it is completed). Preparations for this are ongoing as shown for example by the scheduled installation of the VircoNET software at JCRC (foreseen for the end of 2009). The reference labs play an important role in the development and validation of the algorithm. ART-A also contributes to strengthening the capacity of these Centres of Excellence through specific lab trainings, including GCLP and writing of SOPs.

Furthermore, ART-A aims to strengthen capacity of the other partner clinics by transfer of different levels of the new HIVDR algorithm when it is completed and through training on the correct use of the new technology in clinical practice, including GCLP, SOPs, and sample shipment. These partner clinics play an important role in the development and validation of the algorithm by providing samples.

Table 2: Level of Partnership programme **Associate African partner clinics⁶** at this moment: level at the review marked printed **bold**

Level	1	2	3	4
Components	<i>Epidemiological relevant population and interested investigators</i>	<i>Identified cohort and follow-up capability</i>	<i>Sites with some clinical trial capacity (indicate phase)</i>	<i>Fully capable site for phase I-III trials</i>
1. Investigators	Lacks GCP	GCP exposure	GCP qualified with limited experience	GCP qualified with experience
2. Subjects	Target population identified	Demonstrated ability to follow-up. Community involvement	Demonstrated ability to follow-up. Community involvement formalise	Demonstrated ability to follow-up. Community development Programme
3. Ethics	IRB not yet established	IRB National ethics Committee exists	IRB National guidelines for clinical trials exist	IRB National guidelines for clinical trials exist
4. Laboratories	Access to laboratory facilities	GLP exposure	GLP qualified with limited experience	GLP qualified with Experience
5. Clinical facilities	Ability to measure clinical outcomes	Access to facilities with staff	Adequate facilities and qualified staff	Excellent facilities with qualified staff
6. Data management	Data collection field staff	Some computer infrastructure and basic data-processing skills	Sufficient computer hardware and software Experienced data-processing staff.	Biostatistics, sufficient computer hardware and software. Experienced data-processing staff
7. Sample repository	absent	Some, but temporary/ sporadic	Part of laboratory	Available (cold) chain
8. IPR skills	absent	External qualified advisor available	Some internal qualified skills available	Experienced qualified personnel available within centre
9. Administration	Basic administrative capability	Basic administrative Capability	Accounting and administrative systems available	Well established and audited accounting and admin systems

⁶ Please note that this table applies to the average level of the associated African clinics and includes an indication of GCP and GLP only, as these are the relevant issues for development of a diagnostic test.

GCP/GLP= Good Clinical Practice/Good Laboratory Practice; international quality standards for clinical/laboratory practice.

IRB= Ethical review Board; independent committee of (local) stakeholders and experts who review proposed work plans for ethical implications and whose approval is required prior to start

At the moment, the capacity of the African partner clinics has been improved by exposure to GCP and GLP courses only, which were provided at the Nairobi workshop. It is unclear to the MTR committee what efforts ART-A is undertaking to ensure that this capacity is being strengthened in a sustainable manner, besides upfront selection of the sites. There seems to be no coherent strategy of the ART-A team to ensure that the institutional capacity built remains with and is used at the partner clinics⁷. No incentives are in place for the trainees to sustainably implement the new knowledge within their clinics, for example by training their colleagues.

Staff turnover

For the ART-A programme, six staff members have been employed by ART-A consortium partners: two PhD students (budgeted for in the ART-A programme proposal), two lab staff members at Wits, one post-doc at Virco and one staff member at PharmAccess. One staff member from Wits left the programme to pursue a job in industry and a replacement for him was hired.

The MTR report submitted by the ART-A team mentions that 'researchers on the programme will be offered posts at Wits'. However, during the site visit, it became clear that this may not be the case for all researchers.

Furthermore, ART-A does not have a plan dealing with the high personnel turnover in African countries⁸, affecting the partner clinics and therefore affecting ART-A's training and implementation activities.

Turnover of staff affiliated to the ART-A programme at the African consortium members may also become problematic for the ART-A programme, but it is unclear whether it is discussed within the ART-A team if, and if so, how the ART-A programme could contribute to finding a solution.

Environmental level

The ART-A partnership aims to serve two goals by setting up resistance testing: first public health and second patient care. Resistance tests performed throughout Africa will be an important surveillance mechanism to monitor HIV drug resistance in Africa. Epidemiological data generated through widespread HIVDR testing is expected to support policy makers in taking informed decisions on optimal ART protocols.

In addition, the ART-A programme aims to benefit the quality of care that HIV patients in resource-limited settings receive by improving access to new HIVDR technology as a timely, more informed decision on treatment can be made (provided results of the VL component of the HIVDR test will be available within short time frames).

The first half of the ART-A programme has been mainly devoted to scientific aspects of the programme. With regard to the international scientific environment, several previously independent research lines of African and European institutes have been integrated into one approach within ART-A. Reference samples and protocols from different research institutes have been validated in each others context. Furthermore, the protocols transferred within ART-A will also be made available in the public domain for free use by African service providers.

⁷ In response to this remark, the ART-A team refer to the Field Evaluation Work Plan for the year 2010. This Work Plan was developed after the MTR site visit and covers stepwise approaches to implement and evaluate ART-A protocols in 5 African countries.

⁸ ART-A responded to this comment in the MTR report as follows: "High staff turnover is definitely a very important issue. ART-A aims to contribute to solutions by significantly simplifying the algorithms for HIVDR and VL testing and thus opening possibilities for African healthcare providers to recruit staff from a wider source."

In addition, several new grants have been obtained by the ART-A consortium. For example, a new project funded by NWO/ Schokland, studies the applicability of IPR issues for the ART-A algorithm. An overview of the new grants obtained by the ART-A consortium is provided in the table below.

Sponsor	Amount	Collaborators/ applicant	Supported activities
NWO/ Schokland	€ 150,000	ART-A consortium/ PharmAccess	Build knowledge and capacity on the applicability of IPR to ART-A
Aids Fonds NL	€ 37,000	ART-A PhD student	Evaluation of semi-quantitative viral load test
EDCTP	€ 196,900	JCRC	Evaluation HIVDR in children. This project will benefit from DBS collection developed by ART-A

Table 3. Overview newly obtained and submitted grants related to the ART-A programme.

As yet, the contribution to creating a favourable public health environment is less clear. Through PASER, the ART-A programme is linked to several advocacy options, for example with WHO's HIVResNet. Collaborations within South Africa have been formed with health services partners, civil society (HIV clinician society), R&D public institutes and private partners. International collaborations have been formed with R&D institutes, ICSS and WHO. Links with government are restricted to good contacts with NHLS and research contacts with LifeLab. ART-A aims for South African policy makers to see the ART-A programme as proof of principle that DR testing can be implemented and, most importantly, that this can be done in a cost-effective manner. ART-A does however not have a coherent communication and dissemination strategy which contains a clear plan to discuss ART-A results and their possible benefit to policy with these policy makers in an open and bidirectional manner⁹.

When the algorithm is complete and implemented throughout Africa, it will greatly contribute to monitoring HIV drug resistance in Africa, which will allow policy makers to make informed decisions on the rollout of second and third line ARVs in Africa. The development of a financial mirror image of the algorithm will also greatly contribute to this (see Relevance - Science). However, contacts with policy makers in Africa up to mid-2009 were restricted to South Africa. No formal contacts with international policy makers and other stakeholders had been established yet. Policy makers from six different African countries have been invited to attend a workshop in Lusaka (November 2009) to be briefed on ART-A progress, exchange information, discuss barriers and build consensus on affordable drug resistance tests for Africa. However, ART-A does not have a communication and dissemination plan aimed at the sustainable involvement of these international policy makers with the ART-A programme.

Furthermore, the ART-A partnership does not yet have a coherent plan aimed at sustainable technology transfer, capacity strengthening and implementation of the algorithm at the partner clinics. For example, at JCRC, knowledge from the first workshop was implemented and disseminated within the lab by the workshop participant because it would cut down costs and improve the quality of the work done. It is however unclear whether this new knowledge and techniques are truly embedded within JCRC or whether the commitment of JCRC to ART-A depends on this one person. Furthermore, whilst this approach by the JCRC participant is laudable, ART-A appears to have no consistent plan to make sure that workshop participants from other labs also do this, other than upfront selection of sites and staff. A clear plan

⁹ ART-A responded to this comment as follows: "The first phase of ART-A concentrated on the laboratory work and development of the algorithm. The second phase is aiming at the policy makers. This is exemplified by the concise policy makers workshop in November 2009 in Lusaka. This was timely, since the policy makers themselves indicated that "proof of principle" was the first step to be made, before discussing policy implications. Since, the efforts on reaching out to policy makers have been further strengthened, including recent interviews and advocacy efforts by the PharmAccess PR-team, dissemination of information to the WHO HIVResNet Steering Committee, etc. In this context, the workshop that was organized in June 2009 at the IAS conference in Cape Town contributed to dissemination of information to key stakeholders in the area of HIVDR. For further information, please refer to the attached workplan."

aimed at sustainable technology transfer and capacity strengthening, starting with a small number of reference labs, and later adding other partner clinics if implementation at the first labs proved to be successful and sustainable, has not yet been developed by the ART-A team¹⁰.

The choice of the reference labs and other partner sites has mostly been based on the PASER network. However, as not all PASER sites qualify for the ART-A programme, additional sites are being identified as well. Other sites (handpicked with advice from WHO) have been added to the ART-A network, but it is unclear what the inclusion criteria are for clinics to qualify for participation in the ART-A network and why ART-A requires such a large network of sites¹¹. Furthermore, the commitment of these sites to the ART-A programme and their role beyond supplying samples for the development and validation of the algorithm is unclear.

Some of the sites mentioned in the original ART-A application have dropped out of the network. For example, the clinic in Nigeria, which was planned for to become the reference lab in West Africa, was dropped from the network. No reference lab for West Africa is currently foreseen.

The new sites will be sensitised on HIV DR and will also be trained in working with the algorithm. The Lusaka workshop will be used as a start for this. However, it is unclear whether all clinics represented at the Lusaka workshop will indeed be implementing the algorithm and thus, whether this workshop is fully oriented to their needs. In addition, it is unclear to the MTR committee which capacity will be built at and which technology will be transferred to which partner clinic; ART-A does not appear to have a clear plan outlining this¹⁰.

Conclusion and recommendations of the MTR committee:

Capacity building and technology transfer activities within the ART-A programme can be divided into three phases:

- 1. Technology transfer from private sector partners to public sector partners;*
- 2. Capacity strengthening of and technology transfer from the consortium partners to African Centres of Excellence;*
- 3. Capacity strengthening and technology transfer from the African Centres of Excellence to the other African partner clinics.*

Within phase 1, the ART-A team is well on schedule as shown by the implementation of Virco technologies at UMCU and Wits. Individual capacity building within the consortium is strong, and it is clear that the consortium partners are committed to this goal. However, the MTR committee is concerned for the future employment of the ART-A researchers after ART-A funding has ended.

Within phase 2 and 3, individual capacity of approximately 60 people of prospected Centres of Excellence and other partner clinics has been built through workshops held within the ART-A programme. However, the ART-A programme does not have a clear strategy on ensuring that the trainees actually use and will continue to use this knowledge.

Furthermore, the role of the Centres of Excellence and other partner clinics appears restricted to sending selected participants to the workshop, so the MTR committee fears that the institutional capacity built at these Centres of Excellence and other partner clinics is not sustainable. This should not be left to chance or to the next workshop and ART-A should develop a plan to ensure sustainable capacity strengthening that includes a plan on how to deal with the high staff turnover in Africa.

In addition, the MTR committee thinks that a clear distinction should be made in technology transfer to and capacity strengthening of the Centres of Excellence and of the other partner clinics. Although the MTR committee applauds the ambitious aim of ART-A to implement HIVDR testing in a broad network of partner clinics, the committee thinks it would be wise to plan for implementation at a limited number of reference labs (Centres of Excellence) first. In case implementation at these reference labs is sustainably

¹⁰ The ART-A team refer to the Work Plan 2010 in response to this remark.

¹¹ ART-A responded to this remark as follows: "Upon recommendation by the MTR committee the ART-A team has now limited implementation according to the 2-5-10 strategy: 2 reference sites with full algorithm, 5 with semi-quantitative VL and 10 with DBS technologies.". This strategy is described in the Work Plan 2010.

achieved, then the technology can be transferred from these Centres of Excellence to the other partner clinics.

A clear strength of the ART-A programme is its link to several advocacy options through PASER, for example with WHO's HIVResNet, and the strong connections within South Africa, for example with policy makers. However, currently contacts with policy makers are restricted to South Africa only. Although the MTR committee applauds the scheduled attendance of policy makers from six African countries at the November 2009 workshop in Lusaka, the committee also thinks that involvement of policy makers in the programme should not be restricted to attending a workshop and that an implementation plan that involves Ministries of Health of the different African countries should be developed.

Therefore, the MTR committee recommends ART-A to:

- Continue the successful approach to transfer technology from private to public partners and expanding the capacity of the African consortium partners. In addition, a plan for the ART-A researchers after the ART-A funding has ended should be agreed upon by the consortium partners¹²;
- Develop a strategy to ensure that the individual capacity at regional Centres of Excellence and other partner sites is built in a sustainable manner and that trainees actually use the knowledge and technology provided through ART-A's trainings. This may include involving potential trainees in the development of courses (what knowledge do they need, how do they want to be trained) and development of a plan to ensure use of the new knowledge;
- Develop a strategy to ensure the sustainability of the institutional capacity built within ART-A at regional Centres of Excellence and other partner sites. This strategy should include, but not be limited to:
 - A plan to ensure institutional use of new knowledge and techniques, for example by inclusion of internal audit mechanisms in trainings and through follow-up site visits after trainings for monitoring and supervision, or external quality assessments. A train the trainers approach, in which people from the regional Centres of Excellence are trained to become trainers themselves so they can spread the knowledge to the other partner clinics, is recommended as it will most likely ensure commitment and actual use of the new knowledge at the Centres of Excellence. CLS could play an important role in designing such courses and facilitating the process of gaining autonomy in implementing the acquired skills (GCLP course -> accreditation -> increased ability to attract own projects) ;
 - Network opportunities and exchange programmes between Centres of Excellence and other partner clinics;
 - Discuss strategies to retain trained staff (for example including a network of strong partners, creating a sense of ownership, and building capacity to access funds to continue research);
 - A plan for continuation of the trainings after ART-A has ended¹³;

This strategy could also take into account the potential role of other networks (such as the East African Community or EDCTP) can play in the identification of needs of clinics; inclusion of go-no-go moments and identified constraints; exploration of the potential role MSc and PhD students could play; and the need for a clear SWOT-type analysis in the development of this plan;

- Develop a stepwise implementation plan, restricting the first step to a limited number (for example, 4 or 5) of reference labs and focus all efforts on sustainable technology transfer and capacity building to those sites to create regional Centres of Excellence. These sites can then assist other partner clinics in implementing the algorithm. This stepwise plan should include go-no-go decision points and moments for evaluation. In this way, ART-A can avoid stretching themselves too thinly, the reference labs can benefit from the full ART-A attention, and the other partner clinics can benefit from a tried and tested implementation plan and assistance of the Centres of Excellence. Most likely, the current ART-A training budget will not suffice for this

¹² ART-A responded to this recommendation as follows: "A plan will be developed for ART-A after the funding period has ended."

¹³ ART-A responded to this recommendation as follows: "The ART-A training modules will be part of the regular CLS curriculum."

entire plan. Perhaps it is possible to find some funds elsewhere in the ART-A programme, but most likely, also other donors and partners will need to be sought;

- *Develop an implementation plan strongly involving policy makers from different African countries (starting with policy makers from countries where the algorithm will be implemented first, see above) in the ART-A programme. Commitment of policy makers and other stakeholders is crucial for the sustainable technology transfer, capacity strengthening, implementation and use of the algorithm.*

b) Relevance with regard to science

The scientific focus of the programme is to develop an affordable resistance algorithm for HIV for Africa. As ARTs become more readily available in Africa, levels of HIV drug resistance are increasing and this poses a threat to the success of ART therapy in resource-limited settings. Monitoring and surveillance of HIVDR is therefore important. The currently available HIVDR algorithm is however labour intensive and requires expensive reagents and cold chain storage and transport systems. Thus, the entire DR algorithm is very expensive and there is a need for an easy to use and affordable algorithm for HIVDR in Africa. Epidemiological data generated by the affordable DR test developed by ART-A is expected to be used mostly by health policy makers (surveillance), but may, in the future, also be used by medical practitioners for individual patient management. For individual patient management, the viral load test as developed by ARTA should however also be able to measure quantitative viral loads with a turnaround time of no more than two weeks. Ideally, this test would be able to replace (more expensive) CD4 tests for HIV-infected patient management in the future.

In order to develop this affordable HIVDR test for Africa, the ART-A programme contains three research projects:

1. Development of a convenient sample collection device and extraction protocol to facilitate HIV drug resistance testing in resource limited settings
2. Development of affordable genotypic applications
3. Implementation and optimization of genotypic interpretation systems

Implementation of the results (the algorithm) of the three research projects at the regional Centres of Excellence and other partner clinics is planned to be achieved through project 4, whilst project 5 is aimed at dissemination of information.

Project 1 focuses on the evaluation of the use of dried blood spots as sample collection, transport and storage device for HIVDR testing. The project is determining the optimal conditions: plasma versus whole blood, optimal delivery device, optimal storage conditions, etc. A publication on dried blood spot storage and extraction is in preparation. The project is being performed at and coordinated by Wits.

Project 2 is coordinated by UMCU. The project focuses on the development and evaluation of an integrated and affordable HIVDR genotyping approach. This genotyping assay is being designed so that it will be suitable for all HIV subtypes circulating on the African continent and will be compatible with Virco's antivirogram assay, allowing for a phenotypic interpretation of drug susceptibility. Project 2 is performed by a PhD student at UMCU and at Wits. Within project 2, CRP-Santé is involved in developing an automated and easy-to-use software for editing sequencing data.

Project 3 is coordinated by Virco and is performed by a PhD student who is jointly supervised by Virco and Wits. The project focuses on the interpretation of genotypic sequences. For this, the vircoTYPE HIV-1 genotype interpretation system is being used, which is based on a database of 45.000 matching HIV genotypes and phenotypes and uses linear regression models to predict the phenotypic susceptibility (or resistance) of the virus to each ARV drug available. Project 3 is optimising the assay using a HIV subtype C backbone and will validate this backbone by testing 100 non-B subtype samples in both the B and C subtype backbones. In addition, within project 3, the vircoNET software has been installed at Wits and will be installed at JCRC by the end of 2009. ART-A aims to install this software in multiple partner clinics and Virco will enable testing and validation of the new capacity built. Virco will also provide training in interpretation of the vircoTYPE reports.

The integration of the research projects is ensured through the close scientific relation between the projects and through active and committed involvement of all partners in the three projects. For example, project 2 is coordinated by UMCU. The PhD student researching this project performs part of the research at UMCU and part at Wits, whilst CRP-Santé is developing easy-to-use software for editing of sequencing data for this project. Furthermore, close collaboration with Virco ensures the compatibility of the genotyping assay with the vircoNET phenotyping software. For the other two research projects, the same partners are involved, allowing for easy integration of research results.

Samples that are used to develop and validate the protocol are collected at the partner sites. The DR testing protocol that is being developed with these data will cater for different needs and possibilities of the different clinics. The ART-A consortium uses the assessment system developed by PharmAccess to assess clinic levels. Using this assessment system, different levels of technology transfer (algorithm) and capacity building (teaching DR knowledge and implementation of the algorithm) can be attuned to local needs and possibilities.

Quality assessment of the research projects is done through review of all draft documents within the project team first, and all senior ART-A researchers later. All practical work is done according to GCP and GLP standards and all samples are collected with informed consent and cannot be traced to individuals.

Since the start of the programme, two additional projects have been added to the originally proposed research: (1) the development of a financial mirror image of the algorithm, and (2) a project studying IPR issues.

(1) A pharmaco-economic expert is making a cost-effectiveness analysis of the new ART-A protocols. This project was developed at ART-A's own initiative and is funded by Virco. This model/ analysis will be aimed at country level, as well as individual clinic level and it will model the financial side of resistance testing. If possible, this model will be freely available via the internet. Data generated by this model will be extremely important for the commitment of policy makers to the implementation of the ART-A algorithm. Unfortunately, policy makers are not yet involved in building this model, although this involvement is critical for political commitment and no local researchers or students are yet involved in this project¹⁴.

(2) The IPR project will study IP issues within the consortium and between all project partners (consortium partners and partner clinics). The research will focus on all countries where the algorithm will be used and will study issues related to the end-product (the algorithm) and ownership of collected samples and data. This project aims to develop an IP model that can contribute to the overall aims of ART-A. Two South African postdocs will perform this project (funded by NWO/ Schokland) that started in September 2009.

Conclusion and recommendations MTR committee

The partnership programme is highly relevant with regard to scientific focus. Importantly, the programme is highly focused and contains clear research questions that link to a common objective. The MTR committee thinks that this is an important strength of the ART-A programme. Furthermore, the integration of the three original research projects is very good.

In addition, the ART-A team has initiated interesting and highly relevant affiliated projects since the start of ART-A (IPR and a cost-benefit analysis of the algorithm) pro-actively. The MTR committee applauds these initiatives. An improvement of the cost-benefit analysis may be made by exploring the potential role of African (MSc or PhD) students, policy makers and other stakeholders can play in the development and validation of the cost-benefit analysis.

Therefore, the MTR committee recommends ART-A to

- *Continue on the highly successful scientific path taken by the ART-A consortium;*

¹⁴ The ART-A team responded to this comment as follows: "Upon this recommendation a local MSc from JRCR in Uganda has now been attracted to support the program."

- *Maintain the constructive and creative partnership in identifying possible new and relevant projects contributing to the ART-A objective;*
- *Explore the potential role of (MSc or PhD) students, policy makers and other stakeholders can play in the development and validation of the cost-benefit analysis to further enhance the relevance of the cost-benefit analysis. For example, MSc or PhD students could explore whether this analysis will yield different results for South Africa compared to other African countries such as Uganda, Tanzania or Botswana. Possible funding for such a project could come from the Bill and Melinda Gates Foundation or the Clinton Foundation. Early involvement of policy makers and other stakeholders could play a crucial role in use of results generated by this model.*

2) Efficiency

The ART-A programme is managed using Gantt charts with deliverables and timelines, which were developed and agreed upon by all partners at the start of the partnership programme.

Project 1 is approximately on schedule. The extraction method from DBS has been optimised and 200 samples have been amplified at Wits to test the sensitivity of the extraction procedure. ART-A reported that within project 1, a first publication on a DR assay with good performance in HIV subtype C has been submitted. A second paper on DBS storage and extraction methods is in preparation. In addition, a planned point mutation assay was cancelled due to high variation and a paper will be written on the ineffectiveness of this point mutation assay.

Project 2 is on schedule. Candidate primer sets for amplification have been evaluated, the prototype of the genotyping assay has been tested using reference strains, and CRP has developed sequence editing software, which after testing was installed at Wits and UMCU.

Project 3 is approximately on schedule. The clade C backbone has been optimized for testing and lab protocols from Virco (extraction, amplification and sequencing) have been implemented at Wits, starting with production of amplicons from a selection of 100 patients. Furthermore, VircoNET software has been installed on 3 computers at Wits and 20 persons have been trained and tested. The VircoNET software will be installed at JCRC at the end of 2009.

Thus, scientifically, the programme is approximately on schedule. However, the main concern for the scientific projects at the moment is that the time remaining for the PhD students to finish their theses is insufficient.

Within project 4, a workshop has been held in Nairobi, Kenya in November 2008, parallel to a PASER workshop. At this ART-A workshop, 60 end users were trained on principles of HIV drug resistance, interpretation and use of HIVDR results, affordable HIV diagnostics, and (for some participants) GCLP. In November 2009, a workshop will be held in Lusaka, where 60 end-users and health policy makers from six African countries will be informed about the ART-A programme and discuss the challenges and opportunities for resistance testing in Africa. At this workshop, the intended end-users will also receive training in resistance interpretation skills and adherence, molecular tools for HIV diagnostics, and GCLP. All workshops include pre and post tests and questionnaires, but no mechanisms to ensure sustainable use of the new knowledge are in place.

Within project 5 (Information dissemination and communication), the first edition of the ART-A newsletter was published in July 2009. In addition, the ART-A website was launched. From this website, an electronic version of the newsletter is also available (registration required). Furthermore, a satellite meeting was organised next to the IAS conference in Cape Town in July 2009. In addition, an online literature database is currently under development.

Conclusion and Recommendations MTR committee

Despite the late start of the ART-A PhD students, the scientific part of the ART-A programme is well on schedule. This laudable efficiency indicates the considerable scientific capacity and commitment of the

consortium partners. However, important progress still needs to be made and the main concern is that the remaining time of the ART-A programme is insufficient for the PhD students to finish their theses. Technology transfer and capacity building *within* the consortium (thus, private sector to public sector partners) is well on schedule, as shown for example by the installation of the Virco software at Wits. However, technology transfer and capacity building at the regional Centres of Excellence (reference labs) and other African partner clinics should be improved. Particularly the sustainability of these technology transfer and capacity strengthening activities is a strong point of concern to the MTR committee.

The MTR committee therefore recommends ART-A to

- Continue with the current approach and pace regarding scientific research and technology transfer *within* the consortium (private sector → public);
- Together with all consortium and affiliated partners, develop a plan to improve the sustainability of training and technology transfer to the regional Centres of Excellence (reference labs) and other partner clinics. This plan should be drafted with considerable input from these sites and should include decisions on the levels of training needed for the different affiliated partners, as well as mechanisms to ensure sustainable use of the new knowledge and technologies (see also Recommendations – Capacity Strengthening)¹⁵;
- Draft a plan to ensure that the PhD students can successfully finish their theses after the ART-A subsidy has ended¹⁶.

3) Effectiveness

Two South African PhD students received training through workshops and courses, as well as on-the-job training. In addition, capacity strengthening (and technology transfer) activities within the ART-A consortium (private → public partners) are well underway, as shown for example by the use of Virco's protocols at Wits, resulting in expanded institutional capacity of the African consortium partners. Furthermore, the protocols transferred within ART-A will also be made available in the public domain for free use by African service providers.

At the workshop in Kenya (November 2008), 60 individuals from the African partner clinics received training in principles of HIV drug resistance, affordable HIV diagnostics, clinical interpretation and use of HIV drug resistance results, and (for some participants) molecular GCLP, principles of HIV drug resistance, and introduction to HIV drug resistance testing. It is however unclear to the MTR committee whether these trainings were effective in reaching the goal of sustainable capacity building. For example, there seems to be no coherent strategy of the ART-A team to ensure that the (individual and institutional) capacity built remains within the partner site and that this new capacity is actually being used. No incentives are in place for the trainees to actually use this knowledge.

Although strong links have been made between the consortium and South African health services partners, civil society, R&D public institutes and private partners, no formal contacts with international policy makers and other stakeholders have been established yet.

Conclusions and recommendations of the MTR committee

The ART-A consortium is well on its way to achieve the set goals for private → public capacity strengthening and technology transfer (within the consortium). The consortium is well embedded in the national research for health policy agenda setting South African organizations.

¹⁵ The ART-A team responded to this recommendation as follows: "Plan has been drafted in detail for Uganda and derivatives of this plan will be used for other countries in Africa."

¹⁶ Regarding the remaining time frame for the PhD students to finish their theses, the ART-A team commented: "It is for sure that the time will not be sufficient and solutions to this issue are urgently needed. In general, a 3-year time period, even under ideal circumstances, is insufficient to accomplish a PhD, also in Western settings." "PhD student programs, timelines, deliverables have been drafted and cover time period for the year 2011, ending in 2012."

However, partnering with and technology transfer to African Centres of Excellence and other partner clinics, as well as involvement of health services, has not yet received as much attention as the scientific part of the programme. In order for ART-A to achieve sustainable capacity strengthening and transfer of technology to the Centres of Excellence and other partner sites, this part of the programme will need more attention from the consortium as quickly as possible. Thus, the MTR committee recommends ART-A to

- Concentrate more attention to the capacity strengthening and technology transfer part of the programme, and especially the sustainability thereof, as soon as possible (see also Recommendations in Relevance – Capacity Building).



Highly automated diagnostic lab at Wits

4) Governance, administrative & financial aspects

CPCD is the coordinating scientific institute of ART-A and subcontracts PharmAccess for programme implementation. PharmAccess also coordinates the ART-A programme, and programme management is supported by Gantt charts with deliverables and timelines. A consortium agreement was signed by all consortium partners at the start of the programme, in which amongst others the obligations of each partner are arranged. In addition, collaboration agreements between PharmAccess and all separate consortium partners have been signed, stating reporting and payment procedures. Each consortium partner is responsible for the coordination of one of the ART-A subprojects (UMCU is responsible for coordinating project 2, whereas CRP coordinates project 2b).

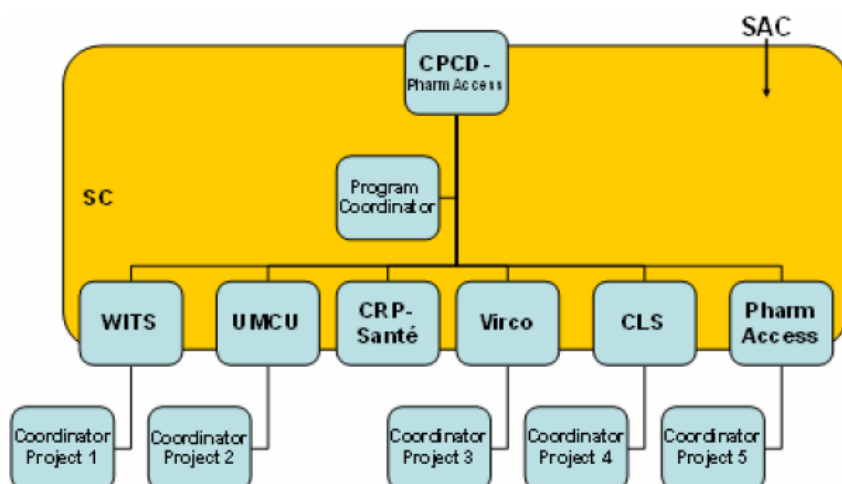


Figure 2. ART-A governance chart

Eight to ten teleconferences per year are held with the consortium partners. One face-to-face meeting was held during the first year, and four were held in the second year. Decisions are made by the

programme Steering Committee (SC). The SC is composed of one representative of each partner (the project coordinator) and is chaired by PharmAccess. The decision-making process of the six ART-A consortium partners is based on a consensus model and leadership is divided equally amongst the partners, especially on the scientific part of the programme (as mentioned by ART-A in the testable goals form, submitted in preparation of the MTR). All major decisions need approval of PharmAccess/ CPCD since the ART-A programme is implemented in conjunction with PASER. African Centres of Excellence and other partner clinics are not part of the ART-A governance structure.

In the original ART-A application, a Scientific Advisory Committee (SAC) is mentioned, to be composed of 2-3 international experts to review the programme annually and provide comments. It is unclear to the MTR committee whether this committee has been established and what the role of this SAC is¹⁷.

Monthly financial reports are sent from the consortium partners to PharmAccess and the programme coordinator and the programme controller together determine the amounts transferred. PharmAccess compares the expenditures with the budget monthly and the ART-A programme is included in each consortium partner's audit. The ART-A consortium has indicated that it is sometimes difficult to achieve 50% spending of the funds in Africa (mentioned in the SWOT analysis drawn up by the ART-A consortium in preparation of the MTR), although NACCAP has not yet received a clear overview of European versus African expenditure of the ART-A programme.

Research documentation within the ART-A programme is done according to GCP standards. All ART-A consortium partners have fully equipped offices.

Conclusion and recommendations MTR committee:

The partnership programme contains strong Northern, Southern and private sector partners, all of which are committed to the ART-A partnership programme. These partners have together created a strong and equal partnership. However, the governance of the programme is mainly aimed at the scientific part of the programme, which is consistent with the finding of the MTR committee that ART-A's focus in its first two years has been mainly on the scientific part of the programme, and no Centres of Excellence or other partner sites are represented in the programme governance. In the future, when more emphasis will be placed on technology transfer to and capacity building at the partner sites and less on scientific research, leadership of the ART-A programme activities may shift a bit to the African consortium partners.

The ART-A consortium indicate that achieving spending the previewed 50% percentage of the funds in Africa is sometimes difficult.

Therefore, the MTR committee recommends ART-A to

- *provide NACCAP with a clear overview of European versus African expenditure over the first two programme years in the annual report of the second year of ART-A and develop a plan to catch up with the set minimum African expenditures in the remaining period;*
- *determine whether a 'capacity strengthening/ technology transfer advisory board' could be composed of representatives from some Centres of Excellence and other partner sites, which can be added to the governance structure (perhaps instead of the SAC) to advise the partnership programme on how best to deal with the capacity strengthening and technology transfer challenges.*

5) Communication and dissemination

Within ART-A, a separate project is aimed at communication and dissemination: project 5 (Dissemination and Communication), which is coordinated by PharmAccess.

This project aims to increase awareness of HIVDR among the non-scientific community and provide the infrastructure for capacity building among African health professionals and scientists for the new HIVDR

¹⁷ The ART-A team responded to this remark as follows: "The SAC has not been formally installed. Regular feedback on ART-A progress was obtained through the PASER meetings of PI's, the PASER SAC's and the WHO HIVResNet fora."

test. Within this project, one edition of a newsletter has been published and a website has been launched. Furthermore, a satellite symposium of the IAS (International Aids Society) conference was organised. During this symposium, the website was launched and around 140 participants were informed about the project.

Communication and dissemination activities have not yet fully started, because for the first half of ART-A's running period, the focus has been on the scientific progress of the programme. For example, an information report to policy makers was postponed in 2008 because in view of the ART-A team not enough relevant information had been collected yet to be presented in the report. In a way, this is understood by the MTR committee, as one cannot communicate a protocol that has not been developed yet. However, to allow for optimal implementation and actual use of the research results (the algorithm), bidirectional communication with policy makers, end users and other stakeholders should be sought as soon as possible.

The ART-A programme aims to contribute to the establishment of one genotyping lab per country. However, even based on the PASER network, it is difficult to identify suitable labs in view of turnover and motivation of staff and available infrastructure (only labs that already have the necessary infrastructure can be included in ART-A). ART-A aims to rely heavily on the website for communication with (potential) affiliated partners and ART-A aims for the website to be a tool in identifying potential partners, as one can enter local information about the lab and receive customized advice, which is then also available to ART-A. It is however unclear whether the potential and currently affiliated partners think this website is the best way to communicate with the ART-A team. It is also unclear why expertise with different website tools (such as EQA databases and blog tools) available within the ART-A consortium are not being used. In addition, it is unclear to the MTR committee in what way the ART-A team communicates with the partner sites to keep them informed on the ART-A progress (besides the once-yearly workshop) and which mechanisms are in place for feedback from the partner sites¹⁸.

Furthermore, although it is clear that PASER and ART-A are strongly linked and that ART-A can greatly benefit from the PASER network, it is also obvious that sometimes the distinction between the two programmes is unclear, as shown for example by comments by several ART-A team members during the MTR site visit.

Conclusion and recommendations of the MTR committee

Up to now, the balance between scientific research and capacity building/ communication and dissemination has been an uneven one in within the ART-A programme. The MTR committee thinks that now would be an excellent time to change the focus of the partnership programme more towards the capacity building/ technology transfer and communication/ dissemination part of the programme and to more closely involve the affiliated partners in doing so. Currently, the MTR committee is concerned with the role of the partner clinics, which appears to be restricted to contributing collected samples for the validation of the algorithm, without possibilities for feedback.

Furthermore, the MTR committee thinks that the ART-A aim to contribute to establishing one genotyping lab per country, although laudable, is rather ambitious and that the ART-A team would perhaps better concentrate their communication and dissemination efforts to creating an infrastructure for the sustainable establishment of a smaller number (3 to 5) of high-quality genotyping facilities.

Therefore, the MTR committee recommends ART-A to:

- *Start focussing the partnership programme more on the communication and dissemination part of the programme. For example, the Lusaka workshop can be used as a starting point to discuss implementation options, strategies and challenges with policy makers and end users in an open and flexible manner. In addition, open and bidirectional communication with the Centres of Excellence and other partner sites could improve the quality of the communication and dissemination plan and help aim it more precisely to their needs;*

¹⁸ The ART-A team responded to this comment as follows: "A regular newsletter is shared with the sites, covering both PASER and ARTA highlights."

- *Develop a forum for receiving feedback from the Centres of Excellence and other partner sites. This will allow for an active discussion on the progress and methods of the ART-A programme, and will ensure commitment of the sites to ART-A¹⁹;*
- *Assess which website tools available within the consortium could contribute to the usefulness of the ART-A website (together with the expected end-users of the website). For example, CLS's blog tool²⁰ or EQA database could be worthwhile improvements to the website. The prospected users of the helpdesk function to be created by ART-A could also be involved in deciding which tool would be most suitable for them as helpdesk tool;*
- *Focus the communication and dissemination efforts regarding the establishment of infrastructure for implementation of the algorithm to a smaller number (4 -5) genotyping facilities in Africa. From that base, a larger implementation plan could be rolled out.*

6. Future of ART-A

Upon request, ART-A drafted an extensive SWOT analysis. This SWOT was adjusted by the MTR committee to include the committee's findings. Please see annex 3 of this report. Strong points of the programme include amongst others: the strong commitment of all consortium partners, including the private partners; the strong political commitment in South Africa; the equality of the partnership; the relevant scientific focus; high research efficiency and integration of the three research projects; technology transfer within the consortium and the addition of two new, relevant, research projects. Weaker points include: the uneven balance between scientific and capacity building priorities; the weak involvement of Centres of Excellence and other partner sites in the governance structure; the fact that contacts with policy makers until now were restricted to SA; the weak dialogue with people outside scientific community (Centres of Excellence and other partner clinics); and the fact that no plan aimed at the sustainability of capacity strengthening activities and phased implementation of the algorithm at the Centres of Excellence and other affiliates sites exists. In addition, points of concern are that the remaining ART-A programme time is insufficient for the PhD students to finish their theses and that the African expenditure percentage may not meet the minimum NACCAP requirements.

Conclusion and recommendations MTR committee

ART-A is a strong network in many respects and most weaknesses identified by ART-A are in line with the findings of the MTR committee. However, the committee is concerned that unless immediate action is taken, the sustainability of ART-A training and technology transfer activities may be much lower than aimed for.

Therefore, to address the weaknesses, the MTR committee recommends ART-A to:

- *Continue with the current approach and pace regarding scientific research and technology transfer within the consortium (private to public);*
- *start focussing the partnership programme more on the technology transfer & capacity strengthening, and communication & dissemination part of the programme;*
- *Develop a stepwise implementation plan, restricting the first step of technology transfer to a limited number (for example, 4 or 5) of reference labs and focus all efforts on sustainable technology transfer and capacity building on those sites, creating local Centres of Excellence. These Centres of Excellence can then assist other partner clinics in implementing the algorithm in a later phase. Local policy makers should also be involved in this plan;*
- *Together with all consortium and affiliated partners, develop a plan to improve the sustainability of training and technology transfer, including strategies to retain trained staff;*

¹⁹ The ART-A team responded to this recommendation as follows: "Affiliated clinics are continuously encouraged to participate in evaluation of protocols and provide feedback in using them. Based on MTR team suggestions a forum will be developed on the ART-A website encouraging interactive discussion amongst users: the "Q&A forum". Furthermore, local centres of excellence will collect feedback and directly link to the ART-A consortium via teleconferences."

²⁰ The ART-A team responded to this recommendation as follows: "This will be explored".

- *More strongly involve the partner sites with the ART-A programme, for example by establishing an advisory board on capacity strengthening;*
- *Draft a plan to ensure that the PhD students can successfully finish their theses after the ART-A subsidy has ended;*
- *Develop a plan to achieve the set minimum African expenditure percentage.*



Members of ART-A and MTR teams on site at CLS

Annex 1: MTR programme ART-A

Monday 28th September 2009		
Time	Subject	Presenter/facilitator
9:00	Coffee	All
9:15	Opening comments	MTR committee
9:30	Governance	Tobias Rinke de Wit
10:00	Efficiency	Nicole Spieker
10:25	Effectiveness	Tobias/Nicole
10:45	Coffee break	
11:00	Information dissemination and communication	Nicole Spieker
11:25	Relevance: science	Carole Wallis
11:55	Relevance: capacity strengthening, technology transfer activities	Charlotte Ingram
12:25	Relevance: capacity strengthening, technology transfer experience	Immaculate Nankya
12:45	Relevance: capacity strengthening, technology transfer activities + the role of Virco	Martin Tuohy
13:15	lunch	
13:45	Leave for Muelmed clinic visit Interview Dr Mariette Botes	Dr Mariette Botes
19:00	dinner	MTR

Tuesday 29th September 2009		
Time	Subject	Presenter/facilitator
9:00	CLS tour (45 min) Interview CLS staff Feroza Bulbulia; Mumtaz Booley; Dr Ute Jentsch	CLS
10:00	WITS tour Interviews key stakeholders <ul style="list-style-type: none"> • Grant Napier and Sibongile Gumbi on IP issues relating to ARTA • PhD student Michelle Bronze 	CLS
11:00	Swot analysis	all
13:00	Lunch (continue SWOT when needed)	
13:30	Interviews policy makers <ul style="list-style-type: none"> • Dr Sagie Pillay: CEO NHLS • Dr Francois Venter: CEO South African Clinicians Society • Assistant dean: Prof. Ahmed Wadee 	Wits University
16:00	Debriefing	MTR
17:30	closing	

Annex 2. SWOT ART-A

Strengths:

- Strong & committed partners, equality of partnership between strong N and strong S partner and private sector
- Science is strong, relevant, efficient and strongly focussed, with clear research questions linking to common objective
- Exchange between projects 1, 2 and 3
- Capacity expansion Wits through technology transfer public -> private (within consortium)
- Contact policy makers SA, strong political commitment SA
- IPR issues and cost-benefit issues will be explored
- Through PASER, link with advocacy opportunities such as WHO's HivResNet

Weaknesses:

- Balance scientific and capacity building priorities uneven
- Scientific capacity strengthening activities appear restricted to SA
- Technical capacity strengthening at Centres of Excellence and other partner sites seems to be restricted to annual workshops
- A stepwise and phased implementation plan for the ART-A algorithm is lacking
- Added value capacity strengthening reference labs (potential Centres of Excellence) unclear
- Dialogue with people outside scientific community (Centres of Excellence and other partner clinics) weak
- Contacts policy makers restricted to SA
- PhDs started behind schedule and may not be able to finish in time

Opportunities:

- Equal partnerships with CoE (Uganda, Kenya). Through this, embedding within bigger network
- When resistance data will become available, PEPFAR and other donors will realise the need for second and third line ARVs for Africa

Threats:

- Attempt at implementation at too many sites
- Staff turnover Africa high – need for training remains
- Commitment institutions to take over programme after ART-A funding unclear
- Dependence on PASER

Annex 3. Abbreviations

ARV	Antiretroviral
CoE	Centre of Excellence
CLS	Contract Laboratory Services
DBS	Dried blood spot
Dept	Department
DR	Drug resistance
EDCTP	European & Developing Countries Clinical Trial Partnership
GCP	Good clinical practice
GLP	Good laboratory practice
HIVDR	Human Immunodeficiency Virus drug resistance
ICRH	International Centre for Reproductive Health (Mombasa, Kenya)
IPR	Intellectual property rights
JCRC	Joint Clinical Research Centre (Kampala, Uganda)
MTR	Mid-term review
NACCAP	Netherland African Partnership for Capacity Development and Clinical Interventions against Poverty related Diseases
NHLS	National Health Laboratory Service
PASER	PharmAccess African Studies to Evaluate Resistance
PIF	Personnel Information Form
SA	South Africa
SAC	Scientific Advisory Committee
SWOT	Strengths, Weaknesses, Opportunities, Threats
UMCU	University Medical Centre Utrecht
VL	Viral load (test)
Wits	Witwatersrand University