Fall 12-1-2014

HIV Drug Resistance Among Infants and Children in South Africa: How Efficient is Genotypic Testing?

Ellen Hendrix
SIT Study Abroad

HIV Drug Resistance Among Infants and Children in South Africa:

How Efficient is Genotypic Testing?

By: Ellen Hendrix

Fall 2014

Switzerland: Global Health and Development Policy

Gelise McCullough

Dr. Alexandre Lambert

Franklin and Marshall College

Public Health (Biology)

Acknowledgements

I would like to thank Gelise McCullough, Technical Director for UNITAIDS for her help throughout the study in providing contacts, reviewing drafts, and her sound guidance. This project would not have been nearly as successful without her help. The participation from Dr. Reuben Granich of UNAIDS, Mr. Dudley Tarlton and Mr. Fabien Lefrancois from the UNDP, and Dr. Lisa Nelson from the Global Fund is also greatly appreciated. Each provided valuable information and enjoyable conversation for this paper. Thanks to Dr. Alexandre Lambert and Dr. Heikki Mattila for their advice during the preliminary stages of the project. Both were influential in the narrowing down of the topic. Finally, special thanks to my host family, the Allemanns, for providing me a wonderful living experience while working on this research project and my family for their full support of my studies and travels.

Table of Contents

Abstract

Background: South Africa has the largest prevalence of HIV infection. This epidemic impacts adults as well as the pediatric population. The presence of drug-resistant mutations to antiretroviral therapies among infants and children is on the rise. Few studies have been conducted on this topic.

Objective: The study aims to determine whether drug resistance testing in the form of genotypic testing is cost-effective when deciding whether to switch to a new HIV antiretroviral therapy following drug failure.

Method: An interactive research approach is taken by collecting primary data from experts in this field. Secondary sources including guidelines from the World Health Organization and the South African Department of Health were also analyzed.

Results: This study finds that, at the moment, genotypic testing is not cost-effective and should not be employed in routine primary care clinics.

Conclusion: Although not recommended for routine care, genotypic testing is extremely beneficial when determining the underlining cause of drug resistance and when tailoring individual regimens for patients. A scale-up of the HIV response and a low-cost drug resistance test are needed in order to make it cost-effective.

Key Words: HIV drug resistance, genotypic testing, pediatric, South Africa

Preface

The topic of HIV/AIDS in Sub-Saharan Africa is large and multi-faceted. There is an abundance of existing research available on the causes and determining factors of HIV, along with the biological progression of this virus and the progression as a worldwide epidemic. However, the topic of HIV drug resistance among pediatric populations has had less focus.

My future goal of working in the health sector with the Peace Corps in a French-speaking African country fueled my initial interest in HIV infection in Africa. My interests grew throughout my studies with the School for International Training in Nyon, Switzerland. On September 15, 2014 a presentation was given at UNITAIDS by Mrs. Gelise McCullough. This presentation outlined the market limitations of pediatric antiretroviral therapies along with the wide treatment gap which exists. This debriefing was a key influence in the selection of the topic for this research study. Specifically, I was interested in the stories of young children needing to go on second and third-line therapies due to HIV drug resistance. It struck me as a major problem which must be addressed. The selection to focus on South Africa came during research when I learned that this country has the highest prevalence of HIV infection. I then became curious as to what this middle-income country can do to prevent HIV drug resistance among children and whether genotypic testing could be a cost-effective tool.

Many experts in this field, including those who participated in this study, provided advice throughout the research and writing period. Advice included how to break this topic into chapters and how to approach writing a lengthy research paper. Overall the process of reaching out to experts and securing personal interviews vastly improved my skills as a researcher and academic.

Ellen Hendrix 19/11/14

Introduction

By the end of 2010, there were an estimated 34 million people globally living with HIV/AIDS, a 17% increase from 2001. Of this, 3.4 million are children where 91% of the infected are living in Sub-Saharan Africa (*UNAIDS Data Tables,* 2011). The increase in prevalence is due largely in part to the improvements in the quantity and quality of antiretroviral (ARV) therapies available, as well as the rollout of these treatments in low and middle income countries. While there have been significant advances in HIV treatments and surveillance programs for adults, there remain many obstacles towards achieving parallel success among children infected with HIV. By the end of 2012, an estimated 220,000 South Africa children were in need of antiretroviral therapy (ART) (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010). Efforts have been undertaken by several organizations such as the Joint United Nations Program on HIV/AIDS (UNAIDS), the World Health Organization (WHO) with UNITAIDS, and the Clinton Health Access Initiative (CHAI) towards closing the treatment gap among children. Specific focus has been on improving the market limitations such as cost and availability. Concern for ART in regards to children is exacerbated by the increasing HIV drug resistance. Drug resistance is attributed to many factors including difficulty with therapy adherence and drug absorption along with lack of appropriate viral monitoring systems. These issues are highly prevalent in resource-poor settings such as South Africa. With the limited treatment options available, choosing the correct second-line therapy is critical, yet resistance testing is not readily available country-wide (Zanoni et al., 2012). This study attempts to address the issue of increasing HIV drug resistance among children in South Africa, highlight the South African national response, and explore the methods taken by the international community to prevent drug resistance.

A substantial field of knowledge exists regarding HIV drug resistance among adults, yet there are significantly fewer studies which focus on children. Additionally, HIV treatment for children is vastly different from adults. Challenges exist in the improvement of pediatric ARVs, mainly the fragmentation of the pediatric market. While many ARVs are circulating the market, few have been approved for children. For example, although the drug tenofovir (TDF) has been approved for first-line treatment in adults, there is limited data on the safety of this drug for children; thus, there are no pediatric formulations with TDF to date (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010). There is a dire need for safe, palatable, potent, heat-stable, and fixed-dosed combinations (FDCs) that can be employed in the fight against pediatric HIV (International AIDS Society, 2013). Finally, there is no consensus as to whether drug resistance testing upon surveillance of first-line HIV drug failure is cost-effective for children. The question in focus is whether widespread pediatric drug resistance testing is efficient when determining whether to switch from first-line to second-line therapies or not.

Literary Review

Drug resistance is an evolving field with new studies continually being released on the efficacy of first-line and second-line treatments as well as the implementation of strategies to reduce drug resistance. One approach is to implement resistance testing to detect virological failure. Most commonly used is genotypic resistance testing, which can detect from a blood sample mutations in the HIV virus known to cause resistance to certain ARVs. It is currently being debated whether genotypic testing is cost-effective and whether it should be implemented in routine care. Three studies represent the competing viewpoints on this issue.

A study published in 2012 by Levinson et al. reported on the clinical and financial impact on genotypic testing at first-line ART failure. By using the Cost-Effectiveness of Preventing AIDS Complications International model of HIV, the researchers were able to simulate a South African cohort of HIV-positive adults failing first-line treatment. Their findings suggest that when an individual test cost less than $100 USD, genotype testing becomes extremely cost-saving at a rate of $900 per years of life saved by treatment. However, this efficiency is dependent upon a rate of wild type HIV near 12% and timely results. Their rationale is that without genotypic testing, virological failure prompting a switch to second-line treatment is based on CD4 count. However, patients failing ART with wild type virus often have poor adherence rather than drug resistance. Genotypic testing may distinguish patients with true resistant HIV from those who might benefit better from adherence counseling rather than a switch to expensive second-line therapy (Levison et al., 2013). It is important to note that this simulation was for South African adults rather than children. It is plausible that genotypic testing is not as cost-effective in children.

A 10-year review of the patterns of HIV drug resistance in South Africa conducted by Kiepiela et al. concluded that genotype testing is cost-saving for those failing second-line treatments and cost-neutral for those failing first-line treatments. Due to the results, the researchers suggested that this testing be included in routine care (2014). A possible reason for the neutrality among patients failing first-line is that second-line treatments are becoming more affordable and it may or may not be worth waiting to switch treatments until test results are analyzed. There are several benefits of genotype testing proposed by Lessells et al. in 2013 including most importantly identifying the root cause of virological failure such as poor adherence, interruption of therapy, or poor absorption of the medications (2013).

The final viewpoint is that genotypic testing is not cost-effective. In October 2014, Phillips et al. reported that despite the assumptions of a relatively inexpensive process, resistance testing at first-line failure when deciding whether to switch to second-line therapy was not cost-effective. They used a similar method as Levinson et al. by simulating a model of HIV progression and the effects of ART in a low-income setting. Patients with virological failure but no resistant mutations have better outcomes when they switch to second-line treatment rather than not, because it is extremely hard to change patterns of adherence. In addition, second-line therapies are more forgiving of weaker adherence due to their higher potency (Phillips et al., 2014). A major argument against implementing widespread HIV drug resistance testing in low-income settings is that clinical and institutional infrastructures are already weak. Priority in regards to funds, human resources, and technology should be directed towards testing for the infection and providing treatments.

After a review of this literature, it is clear that there is a lack of consensus regarding the cost-benefit factor of genotypic resistance testing among children providing a rationale for this study.

Research Methodology

In order to answer the research question, primary and secondary sources were gathered using a variety of methods. For secondary sources, a search was conducted on databases such as PubMed, Google Scholar, and Web of Science with the key words “HIV drug resistance”, “Children”, and “South Africa”. These searches revealed many studies conducted on these topics as well as government documents. Two main documents discovered were the “Consolidated Guidelines on the use of ARV Drugs for Treating and Preventing HIV Infection June 2013”

published by WHO and the "South African Antiretroviral Treatment Guidelines 2013" published by South Africa's Department of Health. A comparison was made to determine whether drug therapies in South Africa follow the guidelines of WHO. Primary sources include the personal interviews conducted by the researcher with various experts in the field of HIV drug resistance. Interviewees were first contacted by email to determine whether they were available to participate. These emails contained detailed information including the purpose of the study along with a request for participation by means of an interview ranging from 30 minutes to one hour.

A combination of methods was employed to collect the data, but it was mainly a qualitative approach. The researcher started with observations of the problem, HIV drug resistance among children, and formulated a theory about drug resistance testing from the findings. Interviews were semi-structured in that questions were prepared ahead of time, but the participants were encouraged to take the conversation in different directions so that it was a natural process. In addition, the process of drug resistance was interpreted from the participant's perspective. Although this is a case study of country, it is the researcher's hope that a theoretical generalization can be made with the results so that they can be applicable to not only South Africa but other low and middle-income countries.

All ethical considerations were taken in this study. No harm was inflicted on the research participants and each was given a detailed description of the research prior to involvement. Confidentiality and privacy were ensured by gaining informed consent to use interviewees' names and other identifiable information. Consent was also given before notes were taken. Interviewees had the opportunity to not answer a question or to stop the interview at any time. Special consideration was taken since this study was focused on one country. Information was gathered and analyzed on South Africa strictly for educational purposes without the intent of

embarrassment. Finally, children are a vulnerable population. Although the topic is HIV drug resistance among children, none were used as participants in this research.

Analysis

Pediatric HIV in South Africa

Overall, South Africa has a generalized HIV epidemic, with greater than one percent of the population infected. Although the epidemic has stabilized over recent years, the prevalence rate is still extremely high, at around 19.1% for adults aged 15 to 49 years. Compared to this alarmingly high level, the pediatric prevalence rate among those aged 0 to 14 years was only 2.4 percent in 2012 (Human Sciences Research Council, 2014). However, there is a wide treatment gap among that 2.4 percent living with HIV. In Sub-Saharan Africa, a region accounting for 91% of the global pediatric treatment need, coverage is extremely low at around 21% (*UNAIDS Data Tables,* 2011). With the 2013 estimates now at 360,000 South Africa children living with HIV, there is a clear motivation to provide the necessary treatment (*HIV and AIDS estimates*, 2012).

PMTCT Strategies

In the last decade, there have been strong efforts in South Africa to prevent mother-to-child transmission (PMTCT). These practices include primary prevention of transmission, prevention of unintended pregnancies, and equitable access to testing, counselling, and ART (*Global guidance on criteria*, 2014). In 2002, the South African Department of Health launched national PMTCT programs. Policies have been revised several times with new provisions including a shift towards an increase in infant HIV testing at an earlier age (Barron et al., 2013). At inception of the program, single-dose nevirapine was used as the standard of PMTCT maternal care in South Africa. However, this therapy is strongly associated with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance among HIV-infected infants. When the WHO

recommended combination regimens for these programs in 2006, South Africa scaled up its standards to include these new regimens.

Overall, there has been an evolution in PMTCT strategies to shift towards earlier treatment. Now the preferred therapy for mothers, Option B+ suggests that all pregnant and breastfeeding women with HIV start ART immediately after diagnosis and maintain their therapy for the duration of the mother-to-child transmission risk (*Consolidated Guidelines*, 2013). PMTCT efficacy is strongly dependent on how quickly the mother is diagnosed, whether she continues treatment after birth, and how quickly the infant is tested (G. McCullough, personal communication, October 30, 2014). For these reasons, WHO has identified early identification of HIV-infected children as vital for PMTCT success. When proper PMTCT methods are employed, HIV transmission to the infant is reduced from 35% to about 2 – 20% (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010). By reducing the viral load to undetectable levels in the infected individual, risk of transmission is significantly reduced.

The new PMTCT strategies dramatically reduce the number of children who acquire infection, but among those who do become infected, NNRTI resistance prevalence is high. A study conducted in 2011 in Johannesburg, South Africa included 230 recently infected HIV-positive children under the age of two. Two-thirds of the participants had been exposed to either maternal and/or infant PMTCT. Of those exposed, 56.8% had NNRTI mutations while 14.8% had nucleoside reverse transcriptase inhibitor (NRTI) mutations (Kuhn et al., 2014). One wonders how problems with adherence play a role in the presentation of resistant mutations and whether what drug resistance testing in this study would have revealed.

Finally, with a focus on 22 priority countries including South Africa, WHO created a Global Plan towards the elimination of new HIV infections among children. The goal is to

"reduce the number of new HIV infections among children by 90%" and to reduce the rate of mother-to-child transmission to less than 5% (*Global guidance on criteria*, 2014). There is a clear need to address the millions of infected children so that they can live normal lives, but it also just as important to prevent children from getting infected.

Pediatric HIV Drug Resistance

With the increased access and exposure to ART, the number of infants and children with HIV drug resistance (HIVDR) is on the rise. The study "Pediatric Response to Second-Line Antiretroviral Therapy in South Africa" found that 9.1% of the 880 children involved experienced drug failure to their first-line therapy after a median time of 95 weeks (Zanoni et al., 2012). Since ART is a lifetime treatment, it is alarming that this many children needed to switch regimens so soon after treatment initiation. The cost and pill burden is high for these children requiring second-line treatment, and their therapy options are dramatically limited.

HIVDR among children can result in two ways. Transmitted drug resistance, or TDR, occurs when a drug-resistant strain is spread from mother to infant (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010). A study conducted between 2005 and 2009 suggests that TDR rates vary among South African provinces. The KwaZulu-Natal province has the highest rates with up to 15% of transmitted resistance to the NNRTI drug class (Hunt et al., 2012). These high rates are contrasted with the prevalence in the Western Cape Province at 3.8% (South African National AIDS Council, 2011). This increases the difficulty in universalizing treatment procedures across South Africa.

The other source of HIVDR is acquired drug resistance or ADR. ADR occurs when mutations of the viral genetic code appear following administration of pediatric ART. The HIV virus replicates so quickly that mutations in the genetic composition render the antiretroviral drugs ineffective against those mutated strains. This type of resistance among children is most

commonly attributed to poor adherence, use of suboptimal treatments, or to toxicity and absorption issues. Several studies support the notion that poor adherence to ARTs is a social predictor of virological failure, defined by WHO as a "plasma viral load above 1000 copies/ml based on two consecutive viral load measurements" separated by 3 months of treatment (Barth et al., 2011 & *Consolidated Guidelines*, 2013). Due to the rapid replication of this retrovirus and longevity of treatment plans, mutations will occur, even among those who follow therapy regimens perfectly. In addition there is also the issue that drug resistance can develop at any stage of treatment. Multidrug resistance among children who have taken multiple ART is increasing (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010). With the limited data available, there is little to base national recommendations regarding treatment plans.

Types of HIV Drug Treatments

Among the therapies available are the three classes of antiretroviral drugs including NRTI, NNRTI, and protease inhibitors (PI). In 2013, the WHO updated the Optimal Formulatory List for pediatric HIV medications. This list includes ten drugs with their drug class, suggested formulation, and dosage (UNICEF, 2014). Although a consolidated list simplifies the decision of which ARTs to use, it also limits the options available once a treatment becomes ineffective. Among the NRTIs, the only drug listed by itself as optimal is a thymidine analogue named zidovudine or AZT. This drug is generally well-tolerated among children but has been linked to metabolic complications such as anemia. The other thymidine analogue stavudine or d4T is associated with lactic acidosis and therefore, has been phased out of use since 2010. Two other NRTIs are used among children but are found in fixed-dosed combinations, that is, they are mixed with other drugs to make appropriate formulations for children. Optimal combinations include those of AZT with lamivudine (3TC), a cytidine analogue with a strong safety and

tolerability record, and those of AZT and abacavir (ABC) (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010).

For the NNRTI drug class, the two optimal medications are efavirenz (EFV) and nevirapine (NVP), both often found in FDCs. The final drug class, the PIs, operate by inhibiting the activity of protease, an enzyme used by the HIV during the production of new viral components. The only optimal PI is ritonavir-boosted lopinavir (LPV/r). While LPV/r is regarded as the most appropriate regimen for infants, it is poorly adapted for children in that it is only available in liquid form, has high alcohol content, and is heat sensitive requiring refrigeration (*Better HIV Treatment for Infants*, n.d.).

The difficulties in choosing a medication go beyond possible side effects and toxicity. When picking among a drug class, such as the NRTIs, the first-line choice impacts the availability of drugs that can be used for second-line, should the child need to switch. For instance, since both AZT and d4T are thymidine analogues, failure of either results in the replication of thymidine analogue mutations (TAMs). When multiple TAMs accumulate, the functionality of other drugs as second-line therapies such as ABC is reduced. On the contrary, a child who becomes resistant to ABC on first-line will not have any TAMs and has the option to take AZT or d4T as second-line (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010).

Challenges with Pediatric HIV Care

There are many social and physical challenges to providing the correct care for HIV positive children and ensuring they adhere to their regimens. In South Africa, as in other Sub-Saharan countries, there is a significant lack of human resources. At the forefront is the shortage of staff adequately trained to manage HIV (Meyers et al., 2007). This ultimately leads to the inability to diagnosis and treat children correctly. In this country, around 15% of public health-

care facilities are unable to initiate HIV treatment (Barron et al., 2013). Doctors in these areas must refer patients to other facilities, subsequently increasing the complications for the mother in regards to access to treatment. Currently, there is a lack of good diagnostics with HIV surveillance and monitoring. Improving diagnostic systems is crucial, because when a mother is monitored, health officials can ensure that the child is receiving the correct dosing at the right times.

Other physical factors include limitations in the market for pediatric HIV formulations. The consistent consumption of necessary medication is hindered by the "poor palatability, high pill burden or liquid volume, frequent dosing requirements, dietary restrictions and side-effects" that accompany the available medications (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010, p.78). In addition, formulation is dependent on weight. In settings where resources are limited, caregivers try methods such as halving the dose of adults, yet this is dangerous, because the actual dosage is unknown.

In a series of workshops held in the provinces of KwaZulu-Natal and Gauteng during November 2012, parents and caregivers of children receiving ART identified the main challenges in adhering to medications. One challenge was not understanding the need for taking ART or how to properly administer the regimens. The financing of attending hospitals and other care facilities also greatly affected access to ARVs. Additionally, several parents had difficulty obtaining their child's birth certificate or proving legal guardianship so they could not receive state aid. Final barriers include frequent appointments and lack of confidentiality among health care workers (Ngobeni-Allen et al., 2013). All of these factors expose the need for an integrated health system among the government and care facilities, trained professionals, and adequate resources.

Not only are their problems with human and diagnostic resources, but there are also social factors contributing to the challenges in pediatric HIV care. In many circumstances, the mother is aware of the positive status of her child but disclosing this information to her husband would create many problems within the home. In addition, due to the stigma, discrimination, and anxiety surrounding a diagnosis of HIV, many mothers chose not to disclose the status of their child to their friends or community. As a Technical Director for UNITAID, Gelise McCullough travels to countries to assess the strength of health care facilities. She gave the example of a woman and her HIV positive child living at a hostel in the Kibera village in Kenya. For fear of discrimination, this mother hid her child's medication and gave them haphazardly when no one was watching. Since the therapy was not followed religiously, her child is now on second-line treatment (G. McCullough, personal communication, October 30, 2014).

Another factor to this issue is that drug resistant strains develop quickly in children, and progression of HIV occurs rapidly during the first few months of an infant's life. In a South African study conducted in 2008, up to 80% of infected infants well at 6 weeks of age had progressed by 12 months of age to become eligible to start an ART (Volari et al., 2008). Another study conducted in Mali on HIV positive children observed that nearly 25% of the cohort developed resistance to HIV after 6 months on ART (Germanaud et al., 2010). Once again, appropriate diagnostics at an early age are necessary in order to get children started on ART as soon as possible. With the greater push to initiate ART earlier, there is the unknown of how the virus and treatment will affect the child as he or she grows. Mrs. McCullough notes that adults can have 50 years of life on ART, but this timeline is undetermined for children (G. McCullough, personal communication, October 30, 2014).

It is easy to say that better diagnostics are needed; however, this is difficult to accomplish because infants require different tests than older children and adults. Those older than 18 months can be given a serological test to determine HIV status. This type of test detects any antibodies the patient's body has developed against HIV. However, this test cannot be performed on infants younger than 18 months since the test cannot determine the mother's antibodies from the infant's. For this group, virological tests must be performed. This test detects the molecular components of the HIV including its RNA (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010).

As previously mentioned, HIV prevalence varies among sexes, age groups, and location. Currently in Sub-Saharan Africa, there is terrible adherence among teenagers. Mothers leave their 12 year old children in charge of their own medication which leads to problems down the line. After a few years on treatment, many of these children interrupt their therapies and go on "holidays". This term is taken from an HIV-positive girl interviewed by Mrs. McCullough in Kenya. She explains that many adolescents start to feel better and wonder of a life without HIV medication. This is obviously a major problem since ART is a lifetime treatment and must be taken religiously for it to be most effective (G. McCullough, personal communication, October 30, 2014).

Opportunities for Pediatric HIV Care

At first glance, the challenges seem daunting; however, there are many opportunities for success in regards to pediatric HIV treatment. Despite the treatment gap among children, South Africa has the largest ART program covering nearly 1.79 million patients primarily through the public health sector (Kiepiela et al., 2014). Since this country is classified as middle-income, it is fairly self-sufficient in regards to meeting the health needs of its population. In addition, the governmental response to the HIV epidemic has undergone a "complete transformation". In

2009, President Jacob Zuma broadened HIV drug access to pregnant women and infants and encouraged an earlier initiation of ART. The increased capacity of South Africa to manage HIV is seen in that most of the treatment is now funded by the government (L. Nelson, personal communication, November 17, 2014).

Another advantage is that the fight against pediatric HIV is a consolidated effort among the international community. Among the numerous actors are UNITAIDS, the United States President's Emergency Plan for AIDS Relief (PEPFAR), UNAIDS, the Global Fund, and CHAI. In a combined effort, each can contribute differently in order to maximize the public health impact.

That same cohort of caregivers who identified barriers to ART access and adherence also provided supportive factors towards access. Participants offered that observing the improvement of their child's health after being on ART improved their confidence in administering the regimen and the reasons for adherence. Additionally, attending treatment classes and talking to other parents improved their understanding of ART (Ngobeni-Allen et al., 2013). Lisa Nelson with the Global Fund agrees that peer support and working with communities is vital in increasing adherence. Other suggested strategies for improved adherence include training of health care workers, counselling services and family clinics where mother and child can receive access simultaneously. By increasing support for these women, they are more freely able to accept their status or the status of their child and move on to treatment.

In addition to improving PMTCT strategies, South Africa has also devoted significant resources into other testing and treatment options. In 2004, the South African Comprehensive HIV and AIDS Care, Management and Treatment Plan made highly active ART (HAART) more available to the masses. Two years later, early diagnosis of HIV in infants was made possible

with the introduction of DNA polymerase chain reaction (PCR) testing. Huge strides have been made since then to increase access to the testing. Although PCR testing capacity was only at 27% in 2006, it dramatically increased to 70.4 % in 2011 (Meyers et al., 2007). With a large ART program, the opinions of those immediately impacted by the HIV epidemic, and the increase in diagnostic tools, South Africa is positioned to reduce transmission and improve the quality of lives for those infected.

The National HIV Prevalence, Incidence, and Behavior Survey conducted by the South African Human Sciences Research Council used HIV incidence testing to measure the number of new cases (2014). This novel approach alone shows the increased national ability to monitor this epidemic. Previous surveys only had the ability to measure prevalence, or the number of people infected with the virus. The overall results point to a decline in HIV incidence since its peak in 2005; however, the decline is not as prominent as hoped.

In 2009, Dr. Reuben Granich and his team of researchers from UNAIDS suggested a unique approach towards eliminating HIV infection among the South African population. There modeling suggests that providing universal, voluntary HIV testing and immediate ARV therapy for those who test positive along with existing preventative measures could “reduce the prevalence of HIV to less than 1% within 50 years”; thus, changing the generalized status of the epidemic (Granich et al., 2009). The driving force behind the success of treatment as prevention is that if you can get viral suppression down in a population, than transmission should also be reduced (R. Granich, personal communication, November 7, 2014). This study shows major promise in the future of the HIV epidemic in South Africa, yet it hinges on having access to testing and treatment for all, which is not yet available.

WHO Pediatric ART Guidelines

In an effort to provide universal and comprehensive HIV treatment, the WHO produced the "Consolidated Guidelines on the use of ARV Drugs for Treating and Preventing HIV Infection" in June 2013 as an update of the 2010 guidelines. The influence behind these guidelines is strengthened by the fact that many institutions contributed to their development including the South African Medical Research Council. WHO takes a humanitarian approach towards the HIV epidemic by recognizing access to HIV prevention, treatment, care and support as a universal right to health (2013). It runs in full circle in that the denial of human health rights increases the risk of HIV infection, and "HIV infection increases the risk of human rights violations" (*National Strategic Plan on HIV*, 2012, p.30).

The complexity of pediatric HIV can be seen in the WHO recommended first-line and second-line therapies provided in Table 1. The recommendations are dependent on age, and second-line options are, as previously mentioned, dependent on what first-line therapy was prescribed. Of most importance is the use of a LPV/r-based regimen as first-line ART for all HIV-infected children younger than three years, regardless of exposure to ARVs during a PMTCT strategy (*Consolidated Guidelines*, 2013). Several studies support the recommendations to use LPV/r rather than an unboosted PI regimen. One such study conducted by van Zyl et al. found resistance mutations in 12 of 17 patients on a single PI therapy compared with 1 of 13 patients on an LPV/r-based regimen (2009). Von Wyl et al's study in 2013 further supports the idea that "ritonavir boosted PI regimens allow for more potent viral suppression," because they exhibit a high genetic barrier to resistance (2013). The WHO recommendations are extremely useful for national health departments when making policy; however, the challenges of pediatric HIV care rule in that if certain drugs are not available, they cannot be employed in ARTs, regardless of how optimal they are. In addition the recommendations of a PI-based regimen over

an NNRTI-based regimen are supported by the findings of Pillay et al. Of the 73 patients on a NNRTI regimen, 80% had both NNRTI and NRTI mutations while only 1 in 17 patients on a PI regimen had resistance mutation (2014).

Table 1. Summary of recommended first-line and second-line ARV regimens for children (including adolescents)

	Children (including adolescents)	First-line ARV regimen	Second-line ARV regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	No change[a]
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV
		AZT + 3TC + LPV/r	ABC or TDF[b] + 3TC + EFV
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r[c]
		TDF[b] + 3TC (or FTC) + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC[c] (or FTC) + LPV/r[c]

[a] No change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on the recent approval of the use of EFV in children less than 3 years, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.

[b] TDF may only be given to children >2 years.

[c] ATV/r can be used as an alternative to LPV/r in children older than 6 years.

From the "Consolidated Guidelines on the use of ARV Drugs for Treating and Preventing HIV Infection June 2013"

In addition to advice on what to prescribe, these guidelines also give recommendations on when to initiate ART in children. The major changes from the 2010 edition are that ART should be initiated among infants and children five years of age or less, regardless of WHO clinical stage or CD4 cell count, those older than 5 years of age with a CD4 count ≤500 cells/mm^3, and among all HIV-infected children in WHO clinical stages 3 or 4 regardless of CD4 count (*Consolidated Guidelines*, 2013)

Each of these recommendations has certain important implications. First, for those younger than 5, disregarding clinical stage and CD4 count widely opens access to treatment. Perhaps the most significant change is that in treatment eligibility from a CD4 of ≤350 cells/mm^3 to ≤500 cells/mm^3 for those older than 5 years of age. It is much more inclusive; however, not many countries have the capacity to manage this switch yet as viral load testing is not readily available (G. McCullough, personal communication, October 30, 2014). Weak health care capacity is also a reason for the third recommendation. In regions where viral load or CD4 testing is not readily available, clinical staging is the only diagnostic tool to use.

South African National Guidelines

Even though the WHO guidelines are comprehensive, they are certainly not implemented evenly across all countries. Additionally, it is a lengthy process to develop and implement policy at the national level, and even more time passes before written policies are accurately reflected in program implementation and clinical practice (R. Granich, personal communication, November 7, 2014). Managing these changes, such as the new ART eligibility CD4 count, is difficult for many low and middle-countries. Specifically with this change, the influx of eligible patients puts a strain on the health care system. However, South Africa has been diligent in keeping up with the changes made and its policies are almost in full compliance.

For children under three years of age, the recommended first-line therapy is ABC, 3TC, and LPV/r. For those older than three years of age, it is ABC, 3TC, and EFV. Second-line therapies are also in accordance with the WHO in that the recommended regimen is AZT, 3TC, and LPV/r. The complete suggested regimens for infants and children are outlined in Table 2 (Department of Health Republic of South Africa, 2013). The Department of Health is also following the phase out of d4T by recommending a switch to ABC if viral loads are undetectable.

Table 2. Summary of South African nationally recommended first-line and second-line ART regimens for infants and children

5.2 Standardised national ART regimens for infants and children

First Line Regimen	
All infants and children under 3 years (or < 10kg)	ABC + 3TC + LPV/r
Children ≥ 3 years (or ≥ 10kg)∞	ABC + 3TC + EFV
Currently on d4T-based regimen	Change d4T to ABC if viral load is undetectable If viral load >1000 copies/ml manage as treatment failure If viral load between 50 – 1000 copies/ml – consult with expert for advice
Second Line Regimen	
Failed first line Protease Inhibitor (PI)-based regimen	
Failed first line PI-based regimen	**Recommended second line regimen**
ABC + 3TC + LPV/r	**Consult with expert for advice***
D4T + 3TC + LPV/r	
Unboosted PI-based regimen	
Failed First line NNRTI based regimen (discuss with expert before changing)	
Failed first line NNRTI-based regimen	**Recommended second line regimen**
ABC +3TC + EFV (or NVP)	AZT + 3TC +LPV/r
d4T +3TC + EFV (or NVP)	AZT + ABC + LPV/r
Third line regimens	
Failing any 2nd line regimen	Refer for specialist opinion – Regimen based on genotype resistance testing, expert opinion and supervised care Access to third line ART will be managed centrally by the National Department of Health

∞ Children ≥ 3 years and exposed to NVP for 6 weeks or longer (PMTCT) should be initiated on ABC + 3TC + LPV/r

Taken from the South African National Antiretroviral Treatment Guidelines 2013

In addition to the standardized regimens are the national monitoring procedures for infants and children living with HIV. Routine measurements of weight, height, development, CD4 count, WHO clinical staging, and TB status are performed at initial diagnosis of HIV and at follow up appointments (Department of Health Republic of South Africa, 2013). These protocols are necessary in order to monitor the development of HIV; however, a major problem is getting patients to come to the clinics for follow-up appointments. The long distances from home to clinic and the long lines deter many mothers from bringing their children in for appointments. Despite this, by being in accordance with the WHO guidelines, these national policies will

expand the number of children able to get treatment and will provide support for proper adherence to their therapies (R. Granich, personal communication, November 7, 2014).

South Africa does lag behind the WHO in several areas as portrayed in Table 3. For ART initiation eligibility for asymptomatic people, South Africa plans to move eligibility to a CD4 count of ≤500 cells/mm^3; however, it has yet to be implemented in the national strategy (*The Global Database*, 2014). This exposes the disparities between the Northern and Southern approach to HIV treatment. In the United States and other Western countries, treatment is given at a higher CD4 count, yet in areas where HIV is most prevalent, treatment is not initiated until a lower CD4 count. Similar disparities exist for pregnant women in that Option B+ is the standard for Northern countries while in South Africa, a CD4 count of ≤350 cells/mm^3 is required for ART initiation. Finally, by decentralizing ARV distribution to the community level, more people have access to treatments. This is especially necessary for South Africa since the clinics cannot manage the full demand for ART.

Table 3. A Comparison between WHO and South African National ART Treatment Guidelines

Policy	**WHO Guidelines** (*Consolidated Guidelines, 2013*)	**South African Guidelines** (Department of Health Republic of South Africa, 2013)
ART Initiation Eligibility for Asymptomatic People	CD4 count ≤500 cells/mm^3	CD4 count ≤ 350 cells/mm^3
ART Initiation for pregnant women	Irrespective of CD4 count (Option B+)	CD4 count ≤ 350 cells/mm^3
Frequency of CD4 Monitoring	Every 6 months	12 months of age
Frequency of Viral Load Monitoring	Month 6, 12, 24 and yearly after month 24	Month 6, 12, 24 and yearly after month 24
Nurse Initiation of ART?	Yes	Yes
ARV Dispensing at Community Level?	Yes	No
When to Initiate ART for Infants?	Immediately regardless of ARV exposure	**Exposure to ART**: NVP at birth then daily for 6 weeks **No exposure to ART**: NVP as soon as possible then daily for 6 weeks

NGO Strategies

The multilateral fight against HIV/AIDS includes many actors in the international community including WHO, UNAIDS, UNITAIDS, the United Nations Development Program (UNDP), the Global Fund, CHAI, and PEPFAR. This list is not exhaustive as there are countless others working in collaboration. The intertwining relationships among these organizations are delicate in that desires and interests have to match in order for there to be effective treatment development and distribution, along with policy development.

Although WHO has developed the bulk of international recommendations for HIV ART, UNAIDS provides global leadership in the response against this epidemic. This organization gets some funding from PEPFAR, and there is collaboration with UNITAIDS on providing funds for testing and with CHAI on monitoring the epidemic (R. Granich, personal communication, November 7, 2014). The Global Fund a new funding model as of last year where the ability of a country to pay for health services and their need are dually considered when grants are given. So that countries no longer compete for grants, money is set aside for each country until it can submit a good application for a grant. There are nine active Global Fund grants in South Africa targeted towards HIV/AIDS, all managed by the country coordinating mechanism. This focal point proposes what to do with the money, decides when to apply the grants, and decides who the principle recipients of care are (L. Nelson, personal communication, November 17, 2014).

Many of the projects of UNITAIDS are focused on HIV treatment, and although only one is directly active in South Africa, a lot of the work benefits this country. One of the largest UNITAIDS projects titled “Pediatric HIV/AIDS Project” ran from 2006-2014. With a budget of $418,474,634 USD and CHAI as the lead implementers, this effort has vastly improved the pediatric ARV market. By increasing the confidence in pharmaceutical companies to invest in pediatric ARVs, antiretroviral prices have decreased, and there are more generic medications and

adapted FDCs. The dramatic decrease in pediatric HIV treatments can be seen in Figure 1. In 2006, a leading ARV cost $252 USD while in 2011, this price dropped to $130 USD per patient per year (ppy) “due to high-volume drug purchases” (*Paediatric HIV/AIDS Project*, n.d.). Another major strategy for market intervention includes providing point-of-care and decentralized diagnostics. This is a significant aspect of the “Better HIV Treatment for Infants and Young Children Program” implemented by the Drugs for Neglected Diseases Initiative. Point-of-care treatment, such as portable machines to measure CD4 count, involves moving treatment closer to the site of patient care so that results are received conveniently and quickly (*Better HIV Treatment for Infants*, n.d.). Finally, increasing access to new HIV monitoring technology such as viral load testing and early infant diagnosis will allow medical workers to follow the development of the virus and the effectiveness of drug formulations.

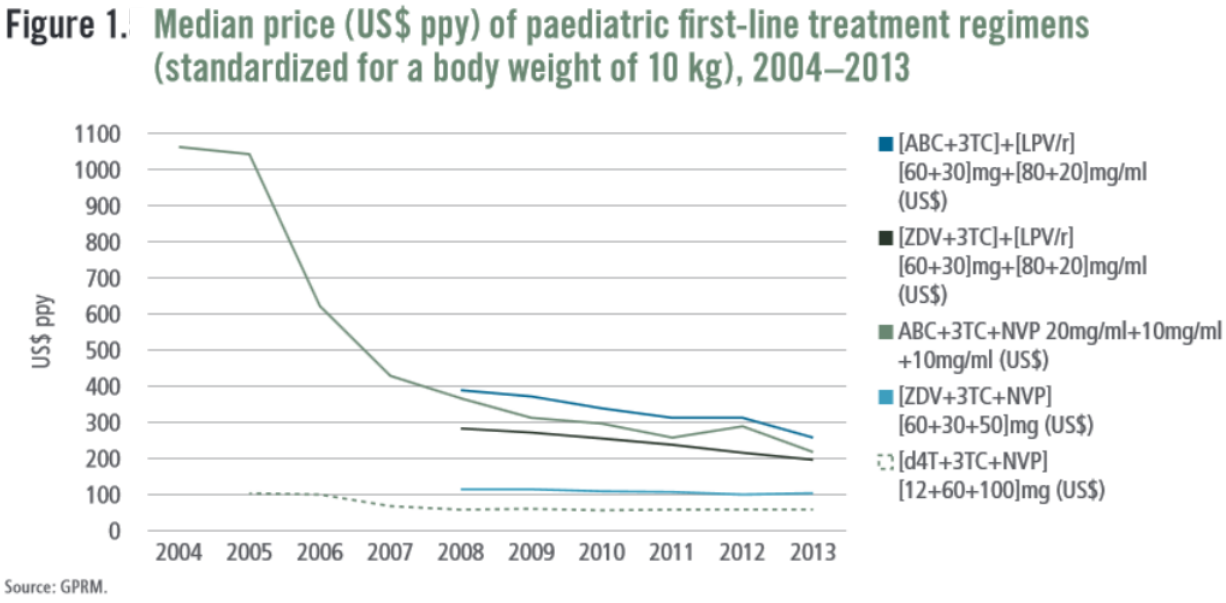

Figure 1. Median price (US$ ppy) of pediatric first-line treatment regimens, 2004-2013

Taken from the Access to Antiretroviral Drugs in Low- and Middle-Income Countries July 2014 Technical Report

Improving the market for second-line treatments is also a key area of work for UNITAIDS. For adult regimens, prices have fallen 73%: In 2006, the leading second-line regimen of TDF, 3TC, and LPV/r cost $1,500 USD ppy. Today, the price is now $527 USD ppy (*Better HIV Treatment for Infants*, n.d.). These advancements are promising in the effort to provide access to every patient in need; yet, it will be interesting to see whether pediatric second-line regimen prices will follow suite in similar reductions. Before this can be accomplished, there needs to be a more competitive market for second-line therapies for children. Finally, WHO has identified several key formulations not available for children including ritonavir-boosted darunavir (DRV/r), a combination that could be used for children failing a first-line regimen based on LPV/r (*Paediatric HIV Treatment Initiative,* n.d.).

WHO and South African Response to HIVDR

In regards to HIVDR, the WHO recommends country-wide surveillance and monitoring systems for the pediatric HIV population (*Antiretroviral Therapy for HIV Infection in Infants and Children*, 2010). South Africa, being more self-sufficient in the HIV fight, has a stronger capacity than most Sub-Saharan African countries to manage these systems. New reports released by the WHO include strategies to support the sustainability of HIVDR surveillance programs. This global strategy encompasses assessment tools for TDR surveys, ADR surveys, and Surveys of HIVDR in infants younger than 18 months of age, all of which require HIVDR genotyping. The goal of each survey is to inform selection of optimal therapies for the target populations (*Meeting Report: Implementation & Sustainability*, 2014).

For TDR, it is recommended that countries incorporate surveillance into existing routine diagnostic testing activities. The ADR surveys will assess levels of viral suppression at two key time intervals: 12-24 months and 48–60 months after treatment initiation. The final survey involving pediatric populations aims to inform selection of optimal first-line ART. Success of

this survey is linked to the strength of early infant diagnostics in that if infants are quickly diagnosed, they can have immediate access to optimal therapies (*Meeting Report: Implementation & Sustainability*, 2014). A question to pose is whether there are any surveillance systems in place to measure HIVDR among children failing first-line ART? If not, is it feasible to initiate such programs into South Africa's health care system?

Included in this report are the draft HIVDR surveillance priorities and plans established by South Africa for 2013-2017. A working group of a clinical team, laboratory group, and epidemiology development group will manage these monitoring surveys. Funding will be temporarily managed by the CDC and Global Fund until they can be "integrated in [the] national health budget". These surveys and genotype testing are a great tool in the mapping of resistance patterns; however, there are several limitations to this approach in South Africa. For example, data in this country is available through over 4,000 clinics, yet many of these clinics operate in paper-based reporting. There is a need to centralize all reporting so that samples are unbiased and reporting is accurate. Additionally, TDR surveys are currently provincial (*Meeting Report: Implementation & Sustainability*, 2014). Many question whether a nationally representative estimate of TDR can be obtained from this method. The solution might be regional surveillance, yet the costs are too large to justify this approach.

Drug Resistance Testing

The idea behind drug resistance testing is that sequencing a virus's genome can be used to optimize the use of ART in individuals experiencing virological failure. This test detects changes in the viral genome, in the form of mutations, which make the individual less receptive to the medication (Imperial College London, 2013). It can also be used to determine whether the underlining issue is drug-resistant mutations or lack of adherence. Although this is an extremely useful tool when tailoring treatments, each of the participatory experts in this study commented

that it is not a cost-efficient option for South Africa at the current moment. A genotypic test today costs about $300. Referring back to Figure 1, one can see that the median price of the recommended pediatric first-line therapy of ABC, 3TC, and LPV/r is slightly more than $250 ppy. Since one test costs more than a year's worth of treatment, it is unlikely that genotypic testing will be implemented nation-wide in the near future. However, if the cost of such tests decreased, there would be more incentive to increase their use. Dr. Nelson identified the need for a low cost strategy with drug resistance testing and provided the example of the rapid GeneXpert test which has had huge success in detecting tuberculosis and Rifampicin resistance (Personal communication, November 17, 2014). Due to the huge issue of mal-adherence, sequencing the genome of the HIV virus would keep patients with perceived virological failure but no resistant mutations from switching to a more costly second-line therapy.

Lessells et al weigh the opportunities and difficulties of implementing widespread HIV genotypic testing. They argue that as more formulations become available for use, the demand for individualized resistance testing will increase to aid clinics in the "management of virological failure." The benefits of drug resistance testing include the conservation of first-line therapies and targeted interventions to resolve adherence issues. They also posit that since third-line therapies are so expensive, it is worthwhile to invest in a genotype test so that the patient has a smaller risk of virological failure (2013).

Over the last decade, laboratory capacity in South Africa has grown tremendously where 17 laboratories now perform nearly two million viral load tests per year. Advancements in the area of resistance testing have been made by The Southern African Treatment and Resistance Network to reduce the cost of sequencing and number of sequencing primers. An expansion of training and teaching for health workers will be required to accommodate for the rise in technical

ability needed (Lessells et al., 2013). Despite the success, it is important to remember that statistics do not always portray the reality of the situation. For instance, it is not only about how many tests are performed, but who is actually being tested (D. Tarleton, personal communication, November 13, 2014. Are the targeted populations, such as young women, being reached by these services?

In one of the largest studies of adult HIV drug resistance in South Africa, 86% of the 222 enrolled participants with evidence of virological failure from a first-line ART regimen had at least one drug resistance mutation. Each participant was given a genotype test to determine the presence of drug resistant mutations. This study conducted fairly recently between December 2010 and March 2012 also reported that one in seven had complex resistance patterns "with the potential to limit the efficacy of the standard second-line ART regimen" (Manasa et al., 2013, p.4). Although some might argue that these resistance tests are unnecessary since the majority of participants had confirmed drug resistance, yet this study reveals that one in seven could have difficulties responding to standard second-line care. Knowing this ahead of time allows medical workers to prescribe a therapy, if the drugs are available, which have the greatest chance of achieving viral suppression (Manasa et al., 2013). The results from this study are widely applicable to South African adults, but can the same be said for infants and children and are there other benefits or complications with genetic testing among a younger population?

Recommendations for South Africa Department of Health

In order to improve performance of ART, testing must be coupled with counseling. With the target for 2016 of 30 million men and women tested and counseled for HIV, South Africa is well on its way to achieving access to both services. Another component of this national strategic plan to end HIV is the bottom-up approach to governance. Reporting and monitoring of HIV will "start at ward level through districts", go to the provincial level through Provincial AIDS

Councils, and end at the national level through the South African National Aids Council. The hope is that a clear framework for policy implementation will guide this entire process (*National Strategic Plan on HIV*, 2012).

One way to address the human rights issue of HIV/AIDS is to tackle the stigma and discrimination associated with a diagnosis. Efforts must be made at the national level for changes to be seen at the provincial and district level. Yet, it is difficult to make laws targeting human behavior. It cannot simply be a regulation against discrimination. There must be proper enforcement which will require a scale-up of existing systems. One suggestion is to use media to raise awareness of this problem. However there are complications with this approach, because individuals might disregard the message, viewing them as inapplicable to their lives. Another suggestion is to increase HIV education and peer support so that the population is more knowledgeable of the epidemic and how discrimination can lead to poor adherence and drug resistance.

Reducing stigma and discrimination is also linked to the idea of prevention as treatment. With the subject of drug resistance, this concept is more upstream. If a mother never got infected, she would never transmit to her kids, and that child would never deal with the problem of HIV drug resistance. Of the billions of dollars spent on HIV in 2012 in South Africa, only 10% was for prevention (Human Sciences Research Council, 2014). South Africa must invest more heavily in preventative measures so that these efforts match those being taken with treatment. Of course, an overall increase in spending on HIV would help the fight against this epidemic, but the issue of funding is always at the forefront.

A significant problem with HIV among the pediatric population in South Africa is that health workers are not finding the children in need (G. McCullough, personal communication,

October 30, 2014). Once the children are found, diagnostic tests can be performed, results given, and treatments prescribed. Of course, each of these areas requires improvement such as faster test results at the site of care and more manageable ARV formulations. Access to testing and treatment would dramatically increase if more medical workers were trained to deliver diagnostic and clinical services. This will require the South African government and Department of Health to increase the amount and quality of training being offered to workers.

An overall simplification of the system might prove beneficial for South Africa. For instance, providing assistance to mothers will help them get their children to the clinics. In addition, clinics where both mothers and children can receive ART simultaneously will incentivize mothers to visit. With the improvement of the pediatric first-line ART market, there is strong hope of similar improvements with second-line and third-line regimens. Third-line regimens are still very much in the clinical stage. They are extremely expensive, costing around $3,500 USD ppy and there are very few options. Their limited availability is problematic for all involved. Mrs. McCullough gave an example of parents splitting pills manufactured for adults in half for their children's ART (G. McCullough, personal communication, October 30, 2014). This is blind dosing, because the active ingredients in the pills are not distributed evenly throughout. Even if a child has access to third-line therapies, the challenges of the regimen are enormous. Some of the infected children Mrs. McCullough has visited in Kenya are taking nine pills in the morning and in the night (G. McCullough, personal communication, October 30, 2014). Simplifying this regimen with fewer pills would lead to better adherence.

Another issue to confront is the lack of studies among pediatric populations. There are many contributing factors behind this including participant accessibility, funding, and ethics. It is difficult to get permission and consent from not only children but their parents in order for them

to be a part of these trials. There is also the question of whether the money funding these studies would be more useful to provide testing and treatment for the millions in need. This plays into the ethical considerations of genotypic testing. Is it ethical to research this new form of testing in Sub-Saharan Africa, a region that needs the technology the most but has the least accessibility? Finally, you must look what ART regimens clinics have. If the stock only includes one first-line and one second-line option, genotypic testing provides no help (R. Granich, personal communication, November 7, 2014).

An alarming recommendation from the WHO 2013 Guidelines is that children on failing second-line regimen with no new drug options should "continue with a tolerated regimen" (*Consolidated Guidelines*, 2013, p.33). The initial step must be the production of third-line therapies. Once this is accomplished, laboratory capacity can be increased and children requiring this level of medication will have higher chances of survival. Yet, there is a debate over whether testing or treatment is more efficient in curving the HIV epidemic. Some argue that resistance testing is not a solution to the problem of drug resistance and advocate for reductions in the emergence and spread of the virus as a means of improving HIV ART programs.

Due to the economic implications, the author does not advise the use of genotypic testing in routine clinical care in South Africa. Several other limitations exist with genotypic testing making it less practical for today including the current fragility of the drug supply chain and the difficulties with "operationalizing" this service into routine care (L. Nelson, personal communication, November 17, 2014). However, the question lingers as to what can be learned from studies involving this type of diagnostics. For instance, what could we learn from a study of 3,000 children given genotypic testing (G. McCullough, personal communication, October 30, 2014)? The funding could come from UNITAIDS and the cohort of children could come from

the Nyumbani Children's Home in Kenya operated by Sister Mary Owens. This children's home already serves thousands of HIV infected children; thus, it would solve the issue of accessing children for studies previously mentioned.

Conclusion

HIV drug resistance among infants and children in South Africa is a multi-faceted issue. The WHO Guidelines revised in 2013 provide many recommendations in regards to HIV antiretroviral testing and treatment for this population. The South African national treatment guidelines are, for the most part, in accordance with the WHO. However with more children eligible for ART, there will naturally be more drug resistance. Many nongovernmental organizations are working in collaboration on the fight against pediatric HIV including UNITAID, UNAIDS, and the Global Fund.

There are many areas of improvement to be made in order to reduce drug resistance. At the forefront is the problem with adherence. Antiretroviral therapies must be taken religiously in order for them to be effective. Also, the longer drug resistance goes undetected, the more amplified the resistance becomes. This problem can be addressed by simplifying the pediatric ARV market and the overall access to medications. Providing formulations in solid form, which taste better, and are heat stable will increase adherence. In addition, peer support and community outreach will encourage mothers to get their children tested and to disclose their status. South Africa is a unique case in that it is middle-income country and has greater laboratory services than neighboring countries. Drug resistance testing is a beneficial tool in that it identifies resistance patterns so that specified regimens can be prescribed for individuals. Yet, in South Africa, resources must first go to providing universal testing and treatment; therefore, this

service is not advisable in routine clinical care. Perhaps the answer lies in providing treatment as prevention, an area of future research with this subject.

Other opportunities for future research with this subject. Once the cost of genotypic testing decreases and when the funding is available, a large study of pediatric HIV drug resistance where the patients are sequenced would be extremely beneficial in the efforts to eliminate HIV. When viral loads are high, transmission and the burden of HIV increases. With drug resistance testing, patients can be put on specialized treatments to solve the problem of mal drug absorption, or their difficulties with adherence can be addressed and managed. The current situation in South Africa does not yet allow from wide-scale genotypic testing, yet, the benefits are definitely worth the efforts to make this diagnostic tool more accessible. Additional future research could include studies on how ART initiated early in life impacts that child physically and mentally as he grows to maturity. Limitations of this study include the lack of new raw data on pediatric HIV in South Africa.

Acronym and Abbreviation List

3TC	Lamivudine
ABC	Abacavir
ADR	Acquired Drug Resistance
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
CHAI	Clinton Health Access Initiative
d4T	Stavudine
DRV/r	Ritonavir-Boosted Darunavir
EFV	Efavirenz
FDC	Fixed-Dosed Combinations
HAART	Highly Active ART
HIVDR	HIV Drug Resistance
LPV/r	Ritonavir-Boosted Lopinavir
NNRTI	Non- Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PDR	Pre-treatment Drug Resistance
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease Inhibitors
ppy	Per Patient Per Year
TAM	Thymidine Analogue Mutations
TDF	Tenofovir
TDR	Transmitted Drug Resistance

UNAIDS Joint United Nations Program on HIV/AIDS

UNDP United Nations Development Program

WHO World Health Organization

Bibliography

Barron, P., Pillay, Y., Doherty, T., Sherman, G., Jackson, D., Bhardwaj, S., …Goga, A. (2013). Eliminating mother-to-child HIV transmission in South Africa. *Bulletin of the World Health Organization, 91*(1), 70-74.

Barth, R., Templeman, H., Smelt, E., Wensing, A., Hoepelman, A., & Geelen, S. (2011). Long-term Outcome of Children Receiving Antiretroviral Treatment in Rural South Africa: Substantial Virologic Failure on First-line Treatment. *The Pediatric Infectious Disease Journal, 30*(1), 53-56.

Department of Health Republic of South Africa. (2013). *The South African Antiretroviral Treatment Guidelines 2013*. Version March 14, 2013. p. 1-13.

Germanaud, D., Derache, A., Traore, M., Madec, Y., Toure, S., Dicko, F., ... Marcelin, A. (2010). Level of viral load and antiretroviral resistance after 6 months of non-nucleoside reverse transcriptase inhibitor first-line treatment in HIV-1-infected children in Mali. *Journal of Antimicrobial Chemotherapy, 65*(1), 118-124.

Granich, Dr. Reuben. Interview by Ellen Hendrix. November 7, 2014. UNAIDS Building Avenue Appia 20, 1211 Geneva 27 Switzerland.

Granich, R., Gilks, C., Dye, C., De Cock, K., & Williams, B. (2009). Universal Voluntary HIV Testing With Immediate Antiretroviral Therapy As A Strategy For Elimination Of HIV Transmission: A Mathematical Model. *The Lancet, 373*, 48-57.

Human Sciences Research Council. (2014). *South African National HIV Prevalence, Incidence and Behaviour Survey, 2013.* Cape Town, South Africa: HSRC Press.

Hunt, G., Ledwaba, J., Basson, A., Moyes, J., Cohen, C., Singh, B., ... Morris, L. (2012). Surveillance of Transmitted HIV-1 Drug Resistance in Gauteng and KwaZulu-Natal Provinces, South Africa, 2005-2009. *Clinical Infectious Diseases, 54*(4), S334-S338.

Imperial College London: Department of Medicine. *HIV-1 Genotypic Drug Resistance Testing*. (2013). Retrieved November 10, 2014.

International AIDS Society-Industry Liaison Forum Industry Roundtable on Paediatric ARVs. (2013, November 23). *Paediatric antiretrovirals: The barriers to and solutions for improved access to optimal drugs in resource-limited settings.* Geneva, Switzerland.

Kiepiela, P., Manasa, J., Moosa, M.Y., Moodley, P., Gordon, M., Parikh, U.M.,… Ramjee, G. (2014) HIV Drug Resistance Patterns at the Epicentre of the HIV-1 Epidemic in Kwazulu-Natal, South Africa 2003-2013. *Journal AIDS Clinical Research,* 5: 299. doi:10.4172/2155-6113.1000299

Kuhn, L., Hunt, G., Technau, K.G., Coovadia, A., Ledwaba, J., Pickerill, S.,…Abrams, E.J. (2014). Drug resistance among newly diagnosed HIV-infected children in the era of more efficacious antiretroviral prophylaxis. *AIDS* 28(11):1673-1678.

Lessells, R., Avalos, A., & De Oliveira, T. (2013). Implementing HIV-1 Genotypic Resistance Testing in Antiretroviral Therapy Programs in Africa: Needs, Opportunities, and Challenges. *AIDS Reviews, 15*(4), 221-229.

Levison, J., Wood, R., Scott, C., Ciaranello, A., Martinson, N., Rusu, C., ... Walensky, R. (2013). The Clinical and Economic Impact of Genotype Testing at First-line Antiretroviral Therapy Failure for HIV-Infected Patients in South Africa. *Clinical Infectious Diseases, 56*(4), 587-597.

Manasa, J., Lessells, R., Skingsley, A., Naidu, K., Newell, M., Mcgrath, N., ... Stoddart, C. (2013). High-Levels of Acquired Drug Resistance in Adult Patients Failing First-Line Antiretroviral Therapy in a Rural HIV Treatment Programme in KwaZulu-Natal, South Africa. *PLoS ONE, 8*(8), E72152-E72152.

McCullough, Gelise. Interview by Ellen Hendrix. October 30, 2014. World Health Organization Avenue Appia 20, 1211 Geneva 27 Switzerland.

Meyers, T., Moultrie, H., Naidoo, K., Cotton, M., Eley, B., & Sherman, G. (2007). Challenges to Pediatric HIV Care and Treatment in South Africa. *The Journal of Infectious Diseases, 196*(3), S474-S481. Retrieved November 10, 2014.

Nelson, Lisa M.D. Interview by Ellen Hendrix. November 17, 2014. The Global Fund to Fight AIDS, Tuberculosis and Malaria. Chemin de Blandonnet 8, 1214 Vernier, Geneva.

Ngobeni-Allen, F., Armstrong, A., Muhe, L., Nelson, L., Penazzato, M., & Shaffer, N. (2013). *Values and preferences – maternal and child health summary*: World Health Organization.

Phillips, A., Cambiano, V., Nakagawa, F., Magubu, T., Miners, A., Ford, D.,…Revill, P. (2014) Cost-Effectiveness of HIV Drug Resistance Testing to Inform Switching to Second Line Antiretroviral Therapy in Low Income Settings. *PLoS ONE* 9(10): e109148. doi:10.1371/journal.pone.0109148.

Pillay, S., Bland, R., Lessells, R., Manasa, J., Oliveira, T., & Danaviah, S. (2014). Drug resistance in children at virological failure in a rural KwaZulu-Natal, South Africa, cohort. *AIDS Research and Therapy, 11*(3).

South African National AIDS Council. (2011, October 27). *Know Your HIV Epidemic (KYE) Report: Review of the HIV Epidemic in South Africa.* Retrieved November 10, 2014, from http://eprints.soton.ac.uk/349081/1/01 KYE Introduction.pdf

South African National AIDS Council. (2012). *National Strategic Plan on HIV, STIs, and TB 2012-2016.* Pretoria, South Africa.

Tarlton, Dudley & Fabien Lefrancois. Interview by Ellen Hendrix. November 13, 2014. UNDP. 11-13 chemin des Anémones, 1219 Châtelaine, Geneva.

UNAIDS. (2011). *UNAIDS Data Tables | 2011.* Retrieved November 10, 2014, from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2225_UNAIDS_datatables_en.pdf.

UNAIDS. (2012). *HIV and AIDS estimates (2012).* Retrieved November 10, 2014, from http://www.unaids.org/en/regionscountries/countries/southafrica/

UNAIDS. (2013). *Global Report: UNAIDS report on the global AIDS epidemic 2013.* Geneva, Switzerland.

UNAIDS. (2014). *The Global Database of National HIV Guidelines*. Last Updated: October 2014. Retrieved November 10, 2014, from https://www.dropbox.com/s/kcb61t13ex4nxqg/GLOBAL%20GUIDELINES%20DATABASE%20October%202014.pdf?dl=0

UNICEF. (2014). *Transitioning to New HIV/AIDS Treatment Regimens-Recommendations to address phase-out of d4T and ddl procurement challenges in the paediatric ARV market. August 2014*. Retrieved November 10, 2014 from http://www.who.int/hiv/pub/paediatric/iatt-who-update-supply-ped-hiv.pdf

UNITAID. (n.d.). *Better HIV Treatment for Infants and Young Children.* Retrieved November 10, 2014, from http://www.unitaid.eu/en/better-hiv-treatment-for-infants-and-young-children.

UNITAID. (n.d.). *Paediatric HIV/AIDS Project.* Retrieved November 10, 2014, from http://www.unitaid.eu/en/paediatrics.

UNITAID, Medicines Patent Pool, & DNDi. (n.d.). *Paediatric HIV Treatment Initiative: Closing the Treatment Gap Through Innovation.* Retrieved November 10, 2014, from http://www.unitaid.eu/images/publications/PEDS_ARV_INITIATIVE_HR.PDF.

van Zyl, G., Merwe, L., Claassen, M., Cotton, M., Rabie, H., Prozesky, H., & Preiser, W. (2009). Protease Inhibitor Resistance In South African Children With Virologic Failure. *The Pediatric Infectious Disease Journal, 28*(12), 1125-1127.

Violari, A., Cotton, M., Gibb, D., Babiker, A., Steyn, J., Madhi, S., ... McIntyre, J. (2008). Early Antiretroviral Therapy And Mortality Among HIV-Infected Infants. *New England Journal of Medicine, 359*(21), 2233-2244.

von Wyl, V., Klimkait, T., Yerly, S., Nicca, D., Furrer, H., Cavassini, M.,… Glass, T. (2013). Adherence as a Predictor of the Development of Class-Specific Resistance Mutations: The Swiss HIV Cohort Study. *PLoS ONE* 8(10): e77691.

World Health Organization. (2010). *Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a public health approach 2010 revision*. Geneva, Switzerland. p. 1-206.

World Health Organization. (2013). *Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a public health approach June 2013*. Geneva, Switzerland. p. 1-269.

World Health Organization. (2014). *Global guidance on criteria and processes for validation: Elimination of mother-to-child transmission (EMTCT) of HIV and syphilis*. Geneva, Switzerland: WHO.

World Health Organization. (2014). *Meeting Report: Implementation & Sustainability of HIV Drug Resistance Surveillance in Africa, Cape Town, South Africa 8-10 July 2013*. doi:10.1371/journal.pone.0077691.

Zanoni, B.C., Sunpath, H., & Feeney, M.E. (2012) Pediatric Response to Second-Line Antiretroviral Therapy in South Africa. *PLoS ONE* 7(11): e49591. doi:10.1371/journal.pone.0049591

Work Journal

10/9/14 **Duration: 0:15**

Today I had my first ISP Advising Session at Ecole Club Migros in Nyon, Switzerland. The meeting was with Dr. Alexandre Lambert. We discussed the preliminary idea for my ISP which was high HIV prevalence among women in South Africa. I was directed towards several NGOs such as UNAIDS for sources of interviews.

10/10/14 **Duration: 0:15**

I had my second ISP Advising Session at the SIT Office in Nyon, Switzerland with Dr. Heikki Mattila. We talked about the final proposal which I had submitted earlier. My topic was still why there is a higher HIV infection rate among women than men in South Africa. I was told that my project passed the ethics review board and that I could begin my research.

20/10/14 **Duration: 4:30**

I started my research today by searching the internet for credible secondary sources in the area of gender and HIV infection in South Africa. This research was complete at my homestay in Bursins, Switzerland.

21/10/14 **Duration: 5:00**

After reviewing the presentation given to our program at the WHO about UNITAIDS by Mrs. Gelise McCullough, I became interested in pediatric HIV. I was so inspired that I changed the topic of my ISP to HIV drug resistance among infants and children in South Africa. I was curious as to some of the determining factors of HIV drug resistance and how this problem is being addressed among pediatric populations. I then researched secondary sources for publications and studies on this topic through journal databases such as PLoS ONE (the Public Library of Science), PubMed.gov, and Web of Science. This was carried out at the UNOG Library, Palais des Nations 1211 Geneva.

22/10/14-27/10/14 **Duration: 32:00**

During this week, I did a lot of research on my topic at various locations including my homestay in Bursins, the UNOG Library at the Palais des Nations, the SIT office in Nyon, and the Starbucks by the Geneva train station. It was a little overwhelming at times, because I was finding a lot of information on HIV infection among children and drug resistance. There was a lot to sort through and some of the dialogue was challenging due to its scientific nature. Throughout this period, I contacted several potential interviewees. On 23/10 I emailed Dr. Martina Penazzato and Mr. Martin Auton from the ARV Procurement Working Group and the World Health Organization. Then on 25/10 I emailed more potential interviewees including Dr. Marc Lallement and Dr. Brian Eley, members of Technical Reference Group on Pediatric HIV Care and Treatment: South Africa. I emailed Mrs. Dorine Da re-van der Wal from the WHO to refer me to Gelise McCullough since I did not have her email from the presentation. Finally, I emailed Dudley Tarlton, who gave our program a presentation on the UNDP's partnership with the Global Fund and their efforts to end HIV/AIDS.

28/10/14 **Duration: 5:30**

Today, I secured my first formal interview with Gelise McCullough, Technical Director for UNITAIDS. We scheduled the interview for Thursday October 30, 2014 at 10:00 at the WHO building in Geneva. I was considering asking her to be my advisor after the interview. I continued writing my paper too.

29/10/14 **Duration: 6:30**

While at the Starbucks in Geneva, I continued my research. I also started writing my paper today. I completed the first draft of my introduction.

30/10/14 **Duration: 2:00**

Today, I had my formal interview with Gelise McCullough at the World Health Organization. Avenue Appia 20 1211 Geneva 27 Switzerland. We sat in the café, drank coffee, and talked about pediatric HIV and the work of UNITAIDS in the WHO cafe. All of my prepared questions were answered and then we spent twenty minutes just discussing more about pediatric HIV in general such as TB co-infection and PMTCT efforts. Hand notes were taken throughout the interview. I learned about her side work where she paints her experiences and uses the profits to

fund children's education. At the end of the interview, Mrs. McCullough agreed to be my advisor and gave me several contacts for more interviews. The two contacts were Dr. Badara Samb with UNAIDS and Francesca Celletti with EGPAF. Afterwards, I reflected on the interview and typed up my transcript. She also told me that the money she would get from being my advisor would be sent to a child in Kenya to fund his/her education which is really exciting!

05/11/14 **Duration: 7:00**

I continued writing my paper and completed the first draft of chapters titled: Pediatric HIV in South Africa, Pediatric HIV Drug Resistance, Challenges to Pediatric HIV Care, and Opportunities for Pediatric HIV Care. This writing occurred in SIT office in Nyon, Switzerland and at the Starbucks in Geneva. I was having trouble finding other interviews since none of the experts I emailed responded.

06/11/14 **Duration: 6:00**

While writing my paper, I received a response from Dr. Samb saying that he was traveling for the remainder of the year but he referred me to Dr. Reuben Granich, a Senior Advisor of Care and Treatment for UNAIDS. I sent an email to Dr. Granich explaining my research and requesting an interview. He responded within several minutes and I set up my second formal interview for the following day at 10:00 at the UNAIDS building. I then continued drafting my paper with the chapter on the WHO Pediatric ART Guidelines and prepared the questions for my interview the next day.

07/11/14 **Duration: 3:00**

My second formal interview was today with Dr. Granich at the UNAIDS building Avenue Appia 20 1211 Geneva 27 Switzerland. Luckily it was across the street from the WHO main building, so I had no trouble finding this location. Questions were prepared but conversation deviated from those topics slightly. I found two WHO technical reports, "Access to Antiretroviral Drugs in Low-and-Middle-Income Countries July 2014" and "Technical and Operational Considerations for Implementing HIV Viral Load Testing July 2014" that I was allowed to take with me for further research. Additionally, I asked if there were any conferences or public events. Dr. Granich said he would invite me to any meetings if there were any in the near future. I returned

to my homestay to type the transcript. Here, after asking about my interview, my host mom told me that our old neighbor, Paula Hacopian (who moved a week after I arrived in Switzerland) worked with the subject of HIV/AIDS. She said she would call and ask if she was available to meet with me.

08/11/14-09/11/14 **Duration: 14:00**

These days were spent writing my paper at the SIT office in Nyon. I worked on the chapters of the South African National Guidelines, NGO Strategies, and the WHO and South African Response to HIVDR. I could not find the phone numbers for the experts who did not respond, so I sent a second email asking if my first had reached their inbox.

10/11/14 **Duration: 6:00**

My host mom gave me Paula's number and said that I could call to schedule a meeting. After several tries, I left a message. Paula called me back while I was working on my paper in the SIT office. She said that she worked with the Global Fund and would contact a colleague who was more knowledgeable in the field of pediatric HIV.

11/11/14 **Duration: 6:30**

I got a response today from Dudley Tarlton, and we set up a formal interview for the upcoming Thursday at 11:00 at the UNDP. I also got an email from Dr. Lisa Nelson, the colleague of Paula Hacopian. Even though she was working in South Africa, she said she would be back in Switzerland the following week. We scheduled the meeting for the upcoming Monday, November 17, 2014. The rest of my time was spent preparing the questions for my interview on Thursday and writing the paper.

13/11/14 **Duration: 2:00**

My third formal interview was today at 11:00 at the UNDP located at 11-13 Chemin des Anémones, 1219 Châtelaine, Geneva with Dudley Tarlton. His colleague, Fabien Lefrancois also joined for the interview. I learned that the UNDP does not deal directly with the Global Fund grants in South Africa but both interviewees provided a lot of helpful information on procurement of grants and how the UNDP works to develop capacity.

16/11/14 **Duration: 4:00**

On my train ride back from Milan, I typed up my notes from my interview on Thursday and added some of that information to my paper. Once I returned home, I edited my paper and prepared the questions for my interview on Monday.

17/11/14 **Duration: 5:00**

I had my final formal interview today with Dr. Lisa Nelson, a Senior HIV Disease Advisor with the Global Fund. Our interview lasted for 45 minutes and was held in the café of the Global Fund building located at Chemin de Blandonnet 8 1214 Vernier-Geneva, Switzerland. She had just been travelling in South Africa and I learned a lot about the global fund grants in this area. After the interview, I returned to my homestay and typed up the transcript. I then finished the first draft of my paper which I emailed to my advisor to edit.

18/11/14 **Duration: 7:00**

In the morning at my homestay, I edited my paper again and completed the interactive research log. I also started my presentation which I will give on Thursday. I decided to use Powerpoint during the presentation. I then went the SIT office in Nyon where I continued my work.

19/11/14 **Duration: 6:30**

After the first day of presentations, I finalized my presentation. My advisor sent her edits back to me today so I was able to make a final revision of my paper. I submitted the final copy to the program director and academic advisor along with my powerpoint presentation.

Interview Transcripts

Interview 1

Interviewee: Gelise McCullough (GM): Technical Director UNITAIDS

Location: World Health Organization Avenue Appia 20 1211 Geneva 27 Switzerland

Date & Time: 30/10/14 at 10:00-11:00

Q: What is your job?

GM: I have worked with UNITAIDS for 6 years. I work on strategy and am a civil society focal point. So I work with those infected a lot. I do a lot of in-country consultations where I meet with those infected, care-givers, and the government to make sure they are working together to strengthen the health care system. I mainly go to medical facilities like hospitals where you can really see the strength of health systems and what is lacking. I have been to many places including Senegal, Liberia, Mali, Kenya, Tanzania, and Myanmar.

Q: Why do children have difficulty adhering to their ARV therapies?

GM: ARV has to be easy and children's ARVs are not. There are weight bands to consider and medicines are hard to take. There are also big difficulties in the market. Currently, LPV/r for infants is only in syrup form which is bad-tasting. So there are three big reasons why children have trouble adhering: 1) it is difficult to take 2) There are social factors involved. Women will know their positive status but their husbands don't so revealing the child's status causes huge problems. As an example, a Kabira woman living in a hostel hid her child's medication and didn't give them religiously. Her child is now on 2nd line treatment. 3) A lack of good diagnostics. When patients are monitored better by health officials, they do better on their treatments.

Q: How close is UNITAIDS in bridging the treatment gap among children?

GM: The good thing about pediatric HIV is that we are not alone. There are many actors working together including PEPFAR, UNAIDS with the political lobby, UNITAD, and the Global Fund. We (UNITAIDS) have the diagnostics but PEPFAR will scale it up because they have a lot more funding. Our public health impact is a combined effort. The treatments are there but we're not finding the children in need. We have been investing in early infant diagnosis which is needed because diagnostic tests are different for children than for adults. (You can't test infants like adults because the mother's HIV virus could be detected instead of the child's). Now there is a push to testing kids as soon as possible, at around 12 weeks. The problem is getting mothers back in for results. Currently only 50% of mothers come back for results. So we need to find the kids, get them diagnosed, get the results, get the kids on treatment, and have better formulations.

Q: How does UNITAID work with other organizations?

GM: The interests and desires of UNITAID, PEPFAR, CHAI and others have to match which is difficult at times. UNITAIDS doesn't work directly with pharmaceutical companies, because we have to keep neutrality in mind so there is no conflict of interests. But we (UNITAIDS) give money to CHAI who gives money to pharmaceuticals.

Q: Do you think drug resistance testing (genotypic testing) before switching treatments is cost-effective? (For instance, to determine if viral load is actually high enough to fail 1st line?)

GM: Not at the moment. It is not viable right now because it costs $300 per test. Sister Mary believes that now, when viral load increases (detected in a test) and there's a switch to second line treatment, this is a blind approach. It is like switching form one blind therapy to another. You don't know what resistant mutations there are or if the real problem is with resistance or adherence. Another huge issue is that kids suffer very quickly from drug resistance. Maybe we (UNITAIDS) could work with Sister Mary and her cohort of children. What could we learn if we paid for 3,000 or so children to get genotype therapy?

Viral load testing is a blood test: how much virus is in the blood? If the virus is undetectable, the medication is working. When the virus is detected, the therapy is either failing or the patient is not taking his/her medications. You can count the number of drugs (pills) too but you can flush them down the toilet. We are now doing a urine test to see if patients are taking their drugs because people lie.

Q: Are there any viable third-line therapies for children?

GM: Not exactly. It's still very much in the clinical stage. Sister Mary in Kenya gets them from compassionate donations (she goes around and asks for treatments). They are so expensive costing around $3,500 per year. People try using adult medication by splitting tablets but the pills are not made evenly. So giving a child half of a pill doesn't mean that you are giving them half the dose. These treatments are not adapted well to children. One child on third line must take 9 pills in the morning and 9 at night. In Sister Mary's cohort, kids have a lot of inherited resistance. Those she treated early on in her program were just given whatever was available and we are now seeing a lot of drug resistance.

Q: How can we reduce drug resistance among children?

GM: - Get testing done quickly and correctly at the start

- Help the mother get to care facilities so she can give the ART to her kids

- Simplifying medications makes it easier to treat kids. How easy would it be to only need to give one pill in the morning?

In the Kenyan orphanage, children would discriminate each other based on how many pills the other would have to take. All the kids have HIV and all are on ART but they are on different programs. One might discriminate another saying "oh he has 4 pills, he's sicker than me".

Q: I was reading that UNITAIDS is only active with one program in South Africa, the "Implementation of CD4 and viral load testing in decentralized, remote and resource-limited settings in MSF HIV programs". Are there any other programs in South Africa?

GM: South Africa is pretty self-sufficient. None of our projects directly go to South Africa but a lot of our work benefit that country.

----------End of prepared questions----------

Q: What about the WHO Guidelines for Treatment?

GM: They are very important. The biggest change was the CD4 count from 500 to 350. Not many countries can manage this switch yet (viral load testing is not readily available). Countries want to switch but don't have the capacity to treat all of those patients. A simplification with Point of Care diagnostics will help. It's not often doctors that are doing the diagnostic work so there needs to be more training.

Q: And the WHO recommendations…?

GM: Breast feeding exclusively. Moms get conflicted because they know they could transmit to their kids if they breastfeed so they switch sometimes to bottle which is worse because it damages the gastro-intestinal tract. Kids are tested at 12 and 18 months to see if viral load is different and see if feeding has given the child HIV.

Q: How efficient is PMTCT?

GM: Birth is always a dangerous affair. There's always a chance of transmission with blood contact between the infant and mom. It often depends on the circumstance whether the kid will be infected. It all depends on how quickly you diagnose the pregnant mom, whether she continues treatment after birth, and how quickly you test the infant after birth. Pregnancy takes a huge toll on the body: energy levels are down and the mother's immunity goes down. When they get sick, they have a higher viral load which means a higher chance of transmitting the HIVV to the child.

The sad reality is that a lot of kids die in Africa. With a mother who loses a child, maybe it is her HIV positive child that dies and she thinks "I'll have another and maybe it will be okay". There is a lot of stigma and discrimination around HIV treatment and diagnosis. For example, it is better if the child is severely malnourished than malnourished. The severely malnourished child will stay in a hospital and get good care while the malnourished child gets extra food and nutrients which the mom gives to all of the children in the family and not just the HIV positive one. The stigma factor is a huge reason why mothers don't get their kids tested.

Q: How does treatment as prevention work?

GM: In discordant relationships, one partner has HIV and the other doesn't. The idea is that if you can get viral suppression down in a group of people, transmission should be reduced. But in Africa, men have multiple partners at a time and have multiple wives. Some wives think they are lucky to have husbands and can't control the sexual actions of their husbands (like ask him to wear a condom etc). So he can go and have sex with others and bring HIV back to his wife. In some relationships, when 1 wife is HIV +, the others want it because that means they are having sex with their husband. Also other STIs are conductors of HIV.

Q: Are there complications with ART?

GM: Another reason why children develop resistance to HIV drugs is due to toxicity and loss to follow up. Adults can have 50 years on HIV treatment but with children, we don't know how long. When you grow up with HIV and on ART, how much effect does the virus have on the child as he grows? Sister Mary notices that there are heart problems with her adult patients that started treatment as kids.

There is terrible adherence with teenagers and specifically boys born with HIV. At 12 years old, mothers disclose care to their kids and let them in charge of their medication. There is also a huge problem with adolescent girls being infected. Lots of work is needed to address this issue such as campaigns to keep them in school and to change laws on child marriage.

Q: Can you talk about the PMTCT efforts?

GM: With PMTCT, we hope to eliminate transmission but there will always be a trickle of kids getting infected. We will never get it down to zero. Now with the B+ option, early antenatal tests that are positive will immediately be put on ARVs (if the mother even goes to antenatal clinic). When viral loads are lower, transmission is lower. We are now working with doctors in Liberia so they can treat HIV themselves rather than referring patients to other doctors.

Q: How does co-infection with TB and HIV affect people?

GM: 1/3 of the population is infected with TB but not all show it and develop it. The TB epidemic is at its peak in Africa. Here, it shows up and develops in this population more than in higher-income countries, because they don't have good sanitation or a stable health care infrastructure. There is a ½ chance of developing TB in people with HIV because they have a suppressed immunity system. TB thrives in these settings and the first killer of people with HIV is TB.

With those who are TB diagnosed, the 1st line treatment is an intensive 2 months (which makes patients feel a lot better) then a continuation for 4 months. However, if the patient defaults in 4 months, there is a nasty multi-drug resistance. There are not good TB drugs on the market as well. More and more, we are finding HIV infected kids by them testing positive for TB. Pediatric TB is a huge problem in Africa. How do we find these children? ½ of them will die before 2 but we are not doing anything to find the other half that live. A solution could be implementing vaccine programs through schools. Example: Juliana wasn't diagnosed HIV positive and started on ART until she was 10 years old!

Interview 2

Interviewee: Dr. Reuben Granich (RG) : Senior Advisor, Care and Treatment

Location: Joint United Nations Program on HIV/AIDS (UNAIDS) Avenue Appia 20 1211, Geneva 27

Date & Time: 07/11/14 at 10:00-11:00

Q: What is your job?

RG: I am an epidemiologist by training but I work as a tactician now. I am from the CDC and have been secunded here. In 2009, my small group published an article in Lancelet. In the article, we argued that if we tested and treated everyone in South Africa, we could eliminate HIV. This was a modelling paper and ruptured the way people thought about treatment. Now, partly due to this paper and others, treatment is not only seen as clinical but as a preventative measure. Your lifespan is near normal when you are put on treatment. Before there are two camps, the testing camp and the treatment camp—they usually worked in separate work streams. Everyone agrees that it is important to get tested in order to know your status. In our paper, we combined the two streams by exploring what would happen if everyone is tested and those who test positive would be put on treatment immediately.

UNAIDS is a multilateral agency working on the global drive of the HIV response. They provide leadership and manage resources.

Q: What are the limitations for pediatric HIV treatment in South Africa?

RG: I am not a pediatric ART expert, but I can see two main limitations. 1) Drug formulations aren't as refined for kids as they are for adults due to issues such as weight bands. 2) There are delivery problems and perhaps the pediatric treatment guidelines make it too complex of a system for treating kids. Just compare the guidelines for children and for adults; the pediatric guidelines are probably more complex. There are also fewer studies involving children and the main advocates for children are their parents.

Pediatric HIV treatment is also somewhat of a downstream approach. We must remember to also focus on upstream interventions. If mothers never got infected, she would never transmit to her kids. It is important to focus on treatment of adults and kids. Option B+ is more of an upstream approach by encouraging all mothers to be on treatment. It was hugely controversial at first. Malawi led the charge, and their initiative was widely successful from the start. Allowing access to treatment for pregnant mothers is a three-for. It keeps the mother healthy, and prevents transmission to their babies and their partners.

Q: Why do children have difficulty adhering to ARTs?

RG: Getting kids to take their medication is difficult. Formulations taste bad and there are a lot to take. Poverty is also a huge issue. Scheduling monthly appointments at the clinic is really difficult for the mothers to do. Often, clinics aren't open long enough and there are longs lines as mothers and children wait for appointments. We must work on designing a system that can reach

everyone. In South Africa, you can't do it all in the clinics. There aren't enough resources for everyone in need to get treatment at the same place every month. There are sociocultural issues to deal with too such as disclosure problems and the stigma and discrimination around a positive diagnosis.

Q: I was looking through the presentations on your dropbox and saw a graph showing that in South Africa, pediatric ART coverage was around 48% while for adults it was around 40%. Why is pediatric coverage higher than adult?

RG: Not sure without looking at the figures, but you also have to be careful of what is actually being calculated. The way coverage is calculated changes when the WHO changes policies regarding treatment. For example, in the past WHO eligibility for treatment was a CD4 count of <200. Now that it is a CD4 count <500, the denominator of who is eligible changes. The real picture is that 35 million people living with HIV will need treatment to remain healthy—without treatment or they will die in 10 years. We have over 13 million on treatment but the remaining people who are not on treatment have about a 10 year lifespan if they do not get treatment. In other words, whether more kids or adults are getting treatment, there is still a large treatment gap for both adults and children. Also there is a cascade. Of all the people with HIV, how many of those know their status? Of those, how many are on ART? And of those, how many have viral suppression? So in the end, what percentage is actually on treatment matters but what is most important is the number of people who are on successful treatment for the long term.

Q: Is drug resistance testing such as genotypic testing an effective tool when deciding to switch from first-line to second-line treatment?

RG: The problem is that this sort of testing is not available to a majority of the world. The tests that are mainly used is the HIV antibody test which shows whether you have been exposed and infected and the CD4 test which is a crude measure of the immune system. Genotype testing is an expensive approach available in wealthier countries and research laboratories but a good one, because when you know resistance patterns, you can tailor responses and treatments. There are ethical considerations too. Do you provide genotype testing for kids or make sure everyone has access to basic HIV and CD4 cell testing? Also, you have to look at what regimens you have. If you only have one first line and one second line option, doing genotype testing may not help since you have limited options to tailor the treatment regimen.

Q: South Africa's national policies for pediatric HIV treatment are concurrent with the 2013 WHO Guidelines to commence ART irrespective of CD4 count. How will this improve ART coverage for more children?

RG: The previous policies often translated into "test and wait". Of course some children were eligible but others were told to wait until they had further immune degradation. If you ask people to wait then they may die or they could come back really sick, get on ART, and then die. People from the community then may say "oh look, ART kills people." It is probably a much better

system now to start the kids right away on treatment. This new policies will expand the number of children able to get treatment and provide support for them to adhere to their therapies. It will also keep the children healthier as well.

Q: How closely to written policies reflect program implementation or clinical practice?

RG: Although some countries have already adapted their policy to the new science, others adapt soon after WHO makes the change. Other countries wait for a while. To develop WHO policies ia a 2-3 year process. It takes 2 years to develop the policies and then can take longer for some countries to adapt to them. You also can't assume that program implementation accurately reflects the policy. When there are changes, governments make shifts and drive new responses within the health system. But this can be a long time period for someone with HIV.

Q: What is the collaboration among UNAIDS and other organizations such as UNITAIDS, the Global Fund, PEPFAR, and CHAI?

RG: It is a complex web of relationships. UNAIDS provides global leadership but also gets funding from PEPFAR so this is a deep collaboration. . There is also a collaborative effort on testing with UNITAID and around monitoring and modeling with CHAI. UNAIDS also works closely with the Global Fund on efforts to fund the response. You could write books about the relationship.

Q: What are the ethical considerations when dealing with HIV treatment among children?

RG: There are many. The main ethical issue usually revolves around the fact that in most places children are less likely to get treatment than adults. Given that children rely on adults for protection and treatment this is ethically wrong. The other ethical dilemma has to do with resources. We have the resources to treat everyone, adults and children, to not do so raises ethical issues. We also spend resources on trials and studies, some for children. These are important but raise ethical issues—should some of these resources go towards treating children. These are just some of the issues we are struggling with in our response.

Interview 3

Interviewees: Dudley Tarlton (DT): Program Specialist, Health and Development UNDP &

Fabien Lefrancois (**FL**): Policy Specialist, Partnership with the Global Fund UNDP

Location: 11-13 Chemin des Anémones, 1219 Châtelaine, Geneva, Switzerland

Date & Time: 13/11/14 at 11:00-11:45

Q: How does the UNDP operate within a country?

FL: We have a partnership with the Global Fund (GF). In countries, we set up a co-PR modality. We act as the interim recipient of the GF grant until the country is capable of managing the funds. Procurement is not easily transferred, but it is a gradual process. You have to meet milestones within a capacity development plan. You also need the resources to develop and implement the grants. Then there is the policy environment where we promote an enabling environment by working with the government. For instance, we assess barriers to access of health (such as men who have sex with men in countries where this is illegal). The eligibility for GP funding depends on income and disease burden. With a higher income, the more focused you have to be on how you spend GF money. Yet the income of the country doesn't necessarily paint the picture for everyone there.

DT: UNDP doesn't deal with the GF grants in South Africa but at a conference I was just at, there was a video playing of the South African minister of health. He said that after looking around and seeing that South Africa was paying more for HIV drugs than neighboring countries, they negotiated price reductions for ARVs.

Q: How does the UNDP develop capacity in countries where it is acting as the interim grant recipient?

DT & FL: We build capacity, then hand it over. We look at different functions to implement GF grants and the status of those functions. Some of the functions are financial, risk management, and MNE. We work with national partners, ministers of health etc. We are the principal recipients of the GF grants but are not in charge of their entire implementation (work with program management embedded in Ministries of Health).

Q: This is country-dependent but do you think the grants are used more for testing or for treatment?

DT & FL: I would imagine more is spent on treatment. With testing, it's not the amount of it but who you test. A country can say they test a million people, but are they reaching the right populations? So we have to target risk populations. There is a limited amount of money and it is hard to scale up response when [WHO] guidelines change. The treatments must be sustainable and now, testing and treatment are sort of being lumped together with the idea of treatment as prevention.

Q: Does UNDP have a role in the HIV drug market?

DT: Not directly. UNICEF procures the medications for the UNDP.

Interview 4

Interviewee: Lisa Nelson, MD (LN): Senior HIV Disease Advisor

Location: The Global Fund Chemin de Blandonnet 8 1214 Vernier-Geneva, Switzerland

Date & Time: 17/11/14 at 14:00-14:45

Q: What is a brief description of your job?

LN: I am a Senior HIV Disease Advisor. Part of my work is internal where we provide guidance to the operation of the Global Fund (GF) grants and part of it is external where we work with partners such as the WHO and UNICEF.

Q: I was looking at the website and saw there are 9 active Global Fund grants in South Africa that deal with HIV/AIDS. Where does the money come from and how is it used?

LN: The GF was started in 2002 by Kofi Annan, former Secretary-General of the United Nations. He saw a major gap in the funding. The GF is a multilateral agency with donors around the world. The biggest donor countries are the United States and France. It started as a performance based fund where countries has to compete for money but there is a new funding model now where we look at the ability of a country to pay and their need. Also money is set aside for each country until that country can submit a good application for a grant.

Q: Do any of these grants deal with pediatric HIV?

LN: The GF set up Country Coordinating Mechanisms (CCM) at country level. We recognize that ministers of health and governments themselves are important in implementing the grants, but we also want the targeted populations to have a role in implementation. The CCM proposes what to do with the money, decides when to apply the grants, and decides who the principle recipients of care are. 60% of the funds go to commodities (ARVs are so expensive).

Q: Is more grant money spent on testing or treatment?

LN: Treatment. The cheapest 1st line, for adults not kids, is still over $100 per patient per year. That doesn't seem like a lot but when you have thousands on treatment, it becomes millions of dollars which is the bulk of the grant.

Q: How is the performance of a grant calculated? (How does one meet expectations?)

LN: When a country writes a grant, they include assessment models in their proposals. The new funding model is that grants are 3 years long so countries are now applying for 2015, 2016 and 2017. There are regular check ins and progress reports. Performance is also monitored against country targets set in the proposal.

Q: How is access to ART increasing in South Africa?

LN: There has been a complete transformation in the way South Africa is dealing with HIV since 2009 when Jacob Zuma became President. The government is now doing more to broaden HIV drug access to pregnant women and infants and to start ART sooner. Most of the treatment is now funded by the government itself.

Q: Can you tell me about HIV drug resistance surveillance in South Africa?

LN: In the USA, if a person tests positive for HIV, you would check drug resistance to tailor a treatment. But many countries lack the resources to provide this. South Africa is somewhere in the middle, because it has higher lab capacity than neighboring countries and it might even have private clinics. The WHO has recommendations to do periodic drug resistance surveys with representative populations.

Q: Is HIV drug resistance (genotypic) testing cost-effective? If not, can it be in the future?

LN: At the moment, it is not feasible to do for each patient. The drug supply chain is fragile and so are health care systems. Everyone gets the standard first line treatment. But even if genotypic testing was cost effective, it would be hard to operationalize all these systems and changes. One hopes there will be a dip stick test (a low cost strategy) for drug resistant HIV to identify mutations. There has been success with TB. The gene expert test detects TB and Rifampicin (the main drug used) resistance. It isn't exactly point of care because it uses electricity but it could be used in the rural setting to test right there. Of course it is still relatively expensive and not available everywhere but with this, a patient can come in, get tested, and be put on a treatment that they will respond well to.

Q: How can we reduce HIV drug resistance among infants and children?

LN: You start with the general population. We know poor adherence is a major factor. There needs to be better treatment options. Right now, formulations for children are hard to take, are in liquid form, and must be taken multiple times per day. Since the PMTCT strategies have increased, more people are on ART so naturally drug resistance will increase. Also before recently, single-dose nevirapine was used and using one drug is a good way to get drug resistance. Now we are going to combination formulations for PMTCT. Before, drugs were less potent and we would say we needed 95% adherence which is really difficult. With drugs being more potent now, they are more forgiving in regards to resistance and we can have a lower percent of adherence. There is also viral load monitoring. WHO recommends monitoring to identify failure quickly. If failure is not found quickly, it will amplify the resistance.

Q: Do you think increasing media efforts and education on HIV would improve adherence for children?
LN: I don't know if mass media efforts will do that much because people think that it doesn't

apply to them. We do know that peer support is very important and so is working with communities. With children, it is harder to hide that they are on ART and harder to hide their status which is a reason why mothers don't get their children tested.

Interactive Research Log

Name: Ellen Hendrix Semester: Fall 2014

Organization	Key contacts	Address	telephone	Brief description of your interactive research	Date(s) & time	Formal/ informal interview
UNITAIDS	Gelise McCullough	World Health Organization Avenue Appia 20 1211 Geneva 27 Switzerland	+41 22 791 1543	Interview at the WHO café. Questions prepared ahead of time were answered, and conversation continued afterwards. Questions pertained to expert's work with UNITAIDS and pediatric HIV. I was given contacts at UNAIDS for other interviews and Mrs. McCullough agreed to be my advisor.	30/10/14 10:00-11:00	Formal
UNAIDS	Dr. Reuben Granich	UNAIDS Building Avenue Appia 20 1211 Geneva 27 Switzerland	+41 22 791 1459	Interview at the UNAIDS building cafeteria. We talked about his work with treatment as prevention and I learned of his modeling study conducted in 2009. I got two reports written by the WHO on HIV drug resistance and HIV medication in low-middle income countries.	7/11/14 10:00-11:00	Formal
UNDP	Dudley Tarleton and Fabien Lefrancois	11-13 Chemin des Anémones, 1219 Châtelaine, Geneva, Switzerland	Dudley Tarleton +41 22 917 82 88	Interview at the UNDP cafeteria. We discussed the role of the UNDP and how their partnership with the Global Fund works.	13/11/14 11:00-11:45	Formal

The Global Fund to Fight AIDS, Tuberculosis and Malaria	Paula Hacopian Dr. Lisa Nelson	Chemin de Blandonnet 8 1214 Vernier-Geneva, Switzerland	+41796070421	I called Paula to arrange a meeting with one of her colleagues. She directed me to Dr. Lisa Nelson.	17/11/14 14:00-14:45	Formal