

**ACCESS TO ART, ADHERENCE AND DRUG RESISTANCE
AMONG HIV-POSITIVE PATIENTS IN RURAL TANZANIA**

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Muktasari

Ugonjwa wa UKIMWI umeathiri takribani watu milioni 70 ulimwenguni kote na kuuu karibu nusu ya watu wote waliokwishambukizwa. Madawa ya kufubaza virusi vya ukimwi vimefanikiwa kuokoa vifo na kufanya waathirika wa UKIMWI kuishi maisha ya kawaida mithili watu wasioambukizwa virusi hivyo. Licha ya mafanikio makubwa kutokana na haya madawa, bado kuna changamoto kadha wa kadha zinazofanya madawa haya yasipatikane au yasitumika kama ilivyokusudiwa. Changamoto hizi ni uhaba/ukosekanaji/uadimikaji wa madawa kwenye kliniki za matibabu, ufuasi mbaya wa madawa na usugu wa virusi vinavyofanya virusi kuendelea kuzaliana japo muathirika wa ukimwi anatumia dawa.

Jukumu la kwanza ilikua ni kutafiti uhaba wa madawa katika wilaya mbili zilizoko nje ya miji mikubwa katika nchi ya Tanzania wakati ambako huduma za UKIMWI zilipokuwa zimesogezwa karibu zaidi kwa wananchi waishio mashambani. Utafiti umeonyesha kuwa katika kipindi cha mwaka mmoja kabla ya utafiti huu, vituo viliishiwa vitenganishi vya upimaji wa virusi vya ukimwi, madawa ya kotrimaksozoli na madawa ya kufubaza virusi vya ukimwi. Katika harakati za kukabiliana na janga hili, baadhi ya mbinu ambazo watumishi wa kliniki na wagonjwa walitumia zingeweza kuongeza matata zaidi kwa wagonjwa wa ukimwi. Tumependekeza ukusanyaji sahihi wa madawa na kutumia taarifa hizo kuagiza madawa kiasi cha kutosha kwa kipindi husika.

Jukumu la pili lilikua ni kutafiti ufuasi wa madawa miongoni mwa waathirika wa ukimwi waliokwisha anza kutumia madawa ya kufubaza virusi vya UKIMWI. Tuligundua kuwa watoto wanaolelewa na walezi wasio wazazi wao walikua katika hatari ya kuwa na ufuasi mbaya kuliko watoto waliokua wanalelewa na walezi ambao pia ni wazazi wao. Wagonjwa walio masikini pamoja na wagojwa waishio karibu na kliniki ya Ifakara walikua na uwezekano mkubwa wa kuwa na ufuasi mbaya wa madawa. Utafiti umezidi kuonyesha kuwa wakati wa msimu wa kilimo watu wengi walionyesha ufuasi mzuri wa madawa kuliko wakati

wa kiangazi. Unyanyapaa dhidi wa waathirika wa ukimwi umeonyesha kusababisha wagonjwa kutokua na ufuasi mzuri wa dawa za ukimwi. Tumependeza kufanyika kwa kampeni za kuzuia unyanyapaa na umezaji wa dawa mbele ya shahidi kwa wagonjwa watoto wenye uwezekano mkubwa wa kua na ufuasi mbaya wa madawa.

Katika jukumu yetu ya mwisho tuliokusudia kutafiti vielelezo vinavyochechea usugu wa madawa ya ukimwi, tumegundua kuwa watu wenye umri chini ya miaka 18 walikuwa na uwezekano mkubwa zaidi wa kuwa na virusi vyenye usugu wa dawa ukilinganisha na watu wenye umri zaidi ya miaka 18. Hii inaweza kua imesababishwa na utoaji wa dawa moja tu (badala ya tatu kama ilivyo sasa) ya nevirapine kwa akina wanawake wajawazito na ufuasi mbaya wa madawa kwa wagonjwa wenyewe. Ili kukabiliana na janga hili tumependekeza kuwa mbinu za kuongeza ufuasi utumike na teknolojia isiyo kuwa ya gharama kutumika katika kufuatilia kuzaliana kwa virusi wakati mhusika anapokua kwenye dawa za ukimwi.

Summary

HIV is one of the worst pandemics in recent times, having affected more than 70 million and with a mortality rate close to 50%. Antiretroviral drugs fight viral replication and has improved life of HIV infected patients since it was introduced. Although ART has the potential of transforming the fatal disease into a chronic condition, there are critical issues surrounding access, adherence and resistance to the drug. We have systematically studied these questions and proposed a way forward to make ART more effective.

The first study explores the stock-out experience in two districts in rural Tanzania at the time when ART decentralization had just taken place. Out of stock was not a strange phenomenon with all sites have experienced stock-out of HIV test kits. The patients in the CTCs experienced HIV drugs and cotrimoxazole stock-out in the year preceding the study. Some of the strategies used appear to aggravate problems.

The adherence studies were showed parental caretaking a strong predictor of adherence in children and poverty and proximity playing acted as barrier to optimal adherence. ART adherence reporting overtime shows, patients tend to have better adherence during agricultural season. De-stigmatization campaigns and Direct Observed Therapy (DOT) interventions to children at risk of non-adherence are may improve adherence.

In our last study on predictors of ART resistance, children were more likely than adults to have resistance mutations. This might be linked with either the previous use of a single dose nevirapine and/or with non-adherence as observed in the adherence study. Improving adherence and low cost viral load monitoring may be appropriate solutions.

1 CHAPTER ONE: Background

1.1 Origin of HIV/AIDS

AIDS was first recognized in the United States of America (USA) in 1981 with reports of unexplained opportunistic infections including *Pneumocystis jirovecii* pneumonia and kaposi sarcoma among homosexual men in New York and San Francisco (Durack, 1981; Gottlieb et al., 1981; Masur et al., 1981). In 1983, a retrovirus called lymphadenopathy associated virus (LAV) or Human T-Cell Lymphotropic Virus III (HTLV III which was later renamed Human Immunodeficiency Virus) that kills T cells was isolated from the lymphatic system of a gay AIDS patient. (Barre-Sinoussi et al., 1983). Further research showed that AIDS is caused by the human immunodeficiency virus (HIV), which originated from non-human primates in Sub-Saharan Africa (SSA) and was transferred to humans during the late 19th or early 20th century. The HIV-1 strain is either closely related to the Simian immunodeficiency virus (SIV) that infects the chimpanzee subspecies *Pan troglodytes troglodytes* (SIV_{cpz}), or to the SIV that infects Western lowland gorillas called SIV_{gor} (Van Heuverswyn et al., 2006). HIV-2 is closely related to SIV from sooty mangabeys (SIV_{SM}). The mutated simian virus became the first HIV (Pickrell, 2006).

Two types of HIV are known: the most common is HIV-1, which is responsible for the worldwide AIDS epidemic, and the immunologically distinct HIV-2 (Clavel et al., 1986). Both viruses have similar transmission routes, cellular targets, and AIDS-defining HIV-related symptoms. However, as compared with HIV-1 infection, HIV-2 infection is characterized by lower transmission rates, a longer asymptomatic stage, a slower decline in CD4+ T-cell counts, and a lower mortality rate (De Cock et al., 1993; Kanki et al., 1994; Marlink et al., 1994; O'Donovan et al., 2000).

The HIV-1 type itself includes four groups M (main), O (outlier), N (non-M, non-O) and P, which have different geographic distributions but produce similar clinical symptoms (Ariyoshi et al., 1999; Burke, 1997; Plantier et al., 2009; Robertson et al., 2000; Vallari et al.,

2011). The M group is further split into 9 subtypes (A through J), as well as at least 58 circulating recombinant forms (CRF) and multiple unique recombinant forms (URFs). HIV-2 is more concentrated in West Africa and can be classified into 8 groups (A–H), with only one CRF, named CRF01_AB, (Ibe et al., 2010) and a novel HIV-2 variant, recently identified in Ivory Coast (Ayouba et al., 2013).

Most of the available epidemiological data indicate that the extensive spread of HIV started in SSA in the late 1970s. By the early 1980s, HIV was found in a geographic band stretching from West Africa across to the Indian Ocean, the countries north of the Sahara and those in the southern cone of the continent remained safe. Currently, countries in North Africa and in the horn of Africa have significantly lower prevalence rates, as their populations typically engage in fewer high-risk cultural patterns that have been implicated in the virus's spread in SSA (UNAIDS, 2010; Velayati et al., 2007). By 1987, the epidemic began gradually to move to southern parts of Africa where some of the most explosive epidemics have been seen in Southern Africa. South Africa has the largest number of people living with HIV/AIDS in the world, 5 million. Botswana and Swaziland have the highest prevalence levels, 38% and 33% respectively. HIV disproportionately affects sex workers, men who have sex with men and people who inject drugs across the world (UNAIDS, 2012b). In Tanzania, the first cases of HIV-1 infection were observed and reported in the Kagera region in 1983 (National Aids Control programme, 2005), and by 2011, it was estimated that 1.6 million Tanzanians were living with HIV/AIDS (UNAIDS, 2012g). The disease has orphaned 1.3 million children. An estimated 150,000 Tanzanians were newly infected with HIV in 2011, which is over 400 new infections every day (UNAIDS, UNAIDS (2012)). In the same year, 83,528 Tanzanians died from AIDS.

1.2. Treatment of HIV/AIDS

1.2.1.1 Antiretroviral Therapy (ART)

After the discovery of HIV/AIDS in 1981, no drug was available to treat the infection until 1987 when Zidovudine was approved by the US Food and Drug Authority (FDA) (Wright, 1986). The drug was used as monotherapy for many years before combination antiretroviral therapy (ART) was introduced 10 years later. To date, there is no cure for HIV/AIDS disease but ART is used to inhibit viral replication thus delaying progression to AIDS. There are Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Fusion inhibitors (FIs), CC chemokine receptor 5 (CCR5) and Integrase inhibitors (INIs). NRTIs, NNRTIs and PIs are the drugs widely available in developing countries. The NRTI slow down the production of reverse transcriptase enzyme and make HIV unable to infect cells and reproduce. The NNRTI (approved in 1997) block the reverse transcription of viral RNA genome in cDNA which is catalysed by reverse transcriptase. The PIs (introduced in 1995) block the protease mediated maturation of released virions. The FIs and CCR5 antagonists block HIV entry into cells. The INIs block the integration of viral genome into the DNA of the host cell.

1.2.1.2 Monitoring of treatment

Low-and middle-income countries (LMIC) have adopted the WHO public health approach as the standard for ART delivery and monitoring of HIV patients (Gilks et al., 2006; UNAIDS, 2012d). The public health approach seeks to ensure the widest possible access to high-quality services at the population level, balancing the best evidence-based standard of care with the feasibility of large-scale implementation in resource-limited settings (Hirschall et al., 2013). This involves scaling up Voluntary Counseling and Testing (VCT), standardizing and simplifying ART and monitoring patients CD4 when possible. CD4 count and viral load are both strong predictors of disease progression and survival regardless of whether a patient is on

treatment or not (Egger et al., 2002; Hughes et al., 1998; Marschner et al., 1998; Mellors et al., 1997; Mellors et al., 1996; Murray et al., 1999; O'Brien et al., 1996; Thiebaut et al., 2000). Since 1996, viral load testing has been a key component of standard care in HIV treatment in developed countries.

1.2.1.3 Benefits of ART

1.2.1.3.1 Suppression of virus

A detectable viral load implies on-going viral replication, which fosters the development of drug-resistant mutations and constitutes a major potential problem for the future of ART (Katzenstein et al., 1996; Lundgren et al., 2002). Drug-resistant strains of HIV selected through lower ART levels can be transmitted to uninfected or drug-naïve patients, leaving them with fewer treatment options (Wainberg et al., 1998). However, despite advances in antiretroviral therapy, some treatments still fail. A major cause of treatment failure is the development of drug resistance in HIV-1 B and non-B subtypes (Clavel et al., 2004; Deeks, 2000; Karmochkine et al., 2000; Miller et al., 1998; Parikh et al., 2012; Praparattanapan et al., 2012; Wainberg et al., 1991). The extreme variability and the high evolution rate of HIV-1 favour the development of antiretroviral resistance. Indeed, HIV-1 infection is characterized by a high degree of genetic variability within infected persons. Although a dose–response relationship between adherence and virologic suppression exists, some patients with high levels of adherence to NNRTI–based ART experience virologic failure, whereas others with suboptimal adherence do not (Bangsberg, 2006; Nachega et al., 2007). This has been interpreted as some drugs (NNRTI) being more forgiving of suboptimal adherence drugs than others (non-boosted PI) as suggested in observational studies and a randomized controlled trial (Bangsberg, 2006; Maggiolo et al., 2005). This is because of the longer half-life and greater potency of NNRTI regimen (Moore et al., 2005; Staszewski et al., 1999).

1.2.1.3.2 Reduction of HIV Transmission

Antiretroviral therapy reduces the risk of HIV transmission by up to 96% (Cohen MS et al., 2011). There are three ways in which these drugs can be deployed to prevent infections: as post-exposure prophylaxis, as pre-exposure prophylaxis, and to reduce infectiousness of HIV-infected people to their sexual partners (treatment as prevention). HIV transmission is reduced at lower viral loads (Gray et al., 2001; Quinn et al., 2000), therefore ART could theoretically reduce HIV incidence and potentially be used to control the epidemic. Once-daily oral administration of the fixed-dose combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) [FTC/TDF; Truvada], which is recommended as part of first-line antiretroviral regimens to treat HIV-1 infection (Adolescents, 2012), is the first (and currently the only) antiretroviral regimen approved (in the USA) for pre-exposure prophylaxis of HIV-1 infection .

1.3 ART challenges

1.3.1 Health system issues

1.3.1.1 Access

Introducing ART particularly to SSA was debated controversially because of concerns about poor infrastructure, logistic, human capacity, cost-effectiveness, adherence and subsequent development of drug resistance (WHO, 2003). However, a feasibility study by the World Health Organization (WHO) about access to ART catalyzed global efforts and ART has been significantly scaled up (WHO, 2010d). In 2006, the member states of the United Nations agreed to aim for universal access (rollout of ART) to treatment in 2010 (WHO et al., 2007). Access to ART in SSA has improved considerably over the past years and has contributed to decreased HIV/AIDS morbidity and mortality in the region (Badahdah et al., 2011; Mills et al., 2011; UNAIDS, 2012e). The global scale-up of ART over the past decade represents one

of the greatest public health achievements of recent times. The number of patients on ART has dramatically increased by more than 26-fold between 2003 and 2011 in resource-limited settings (World Health Organization, 2012). A combination of efforts has made it possible to get nearly ten million HIV positive patients onto ART (AIDS et al., 2008; Mutevedzi et al., 2010; Stringer et al., 2006; Toure et al., 2008) and 54% of people who are eligible for treatment in the developing world receiving ART (UNAIDS, 2012e). Access to pediatric ART in resource limited settings has risen more than 7-fold from 75,000 children receiving ART in low and middle income countries in 2005 to 562,000 by the end of 2011 (WHO, 2013c). This success has accelerated efforts to reach the UNAIDS goal of treating 15 million people by 2015 (PEPFAR, 2012; UNAIDS, 2012f). Two countries in SSA, Botswana and Rwanda, have achieved the universal access target (treatment coverage of 80% or more of patients in need) at the end of 2009 (WHO, 2010d), while countries such as Ethiopia, Zambia, Namibia, and Senegal are moving closer to the target having covered 50–80% of patients in need of treatment (WHO, 2010d). ART was introduced to Tanzania in 1995 with mono and dual regimens available to only a small number of patients due to the high cost of the drugs (Kasang et al., 2011; G. R. Somi et al., 2008). Access to ART has increased since the Tanzanian government launched its public-sector ART program free of charge in October 2004 (Kasang, Kalluvya et al., 2011; G. R. Somi, Kibuka et al., 2008). ART coverage in Tanzania has been steadily rising since 2004, with a coverage rate of 52% by 2012 (UNAIDS, 2012a).

HIV stigma is still a big problem hindering HIV testing and ART use among HIV infected patients. HIV stigma described as prejudice and discrimination that are directed at people with HIV/AIDS (Herek et al., 1998) is a universal phenomenon (UNAIDS, 2002). Disclosure of HIV status open up the potential for stigma and the shame of being HIV positive (Landau et al., 2004) and the experience of disclosing has been documented as traumatic. Stigmatizing

attitudes about HIV/AIDS leading to fears of discrimination can influence decisions to seek HIV testing and HIV treatment services (Hull et al., 1988). AIDS stigmatizing beliefs represent potential barriers to seeking HIV testing (Herek et al., 2003).

1.3.1.2 Procurement supply chain management

With an unabated growth of ART cohorts managed at an ever-increasing number of facilities, procurement and supply chain management (PSM) systems for HIV/AIDS medicines in resource-constrained countries are facing critical challenges, and problems in the PSM systems are becoming a growing concern (Schouten et al., 2011). A WHO survey in 2009 revealed that 38% out of 94 reporting countries had documented at least one stock out of ART in health facilities (WHO, 2010d). Interrupted supply of ART puts individual patients at risk of disease progression and death [3], jeopardizes public health due to development of ARV drug resistance, hampers progress towards universal access, and diminishes the credibility of ART programme in the eyes of patients, the community and healthcare providers. An increase and spread of ART resistance will necessitate a change of first-line regimens, and these are without exception more expensive and increase the costs of national ART programmes.

1.3.1.3 Cost

In the presence of resource constraints, the sustainability of ART access clearly depends on affordable prices for the drug active pharmaceutical ingredients (API). Throughout the 1990s, the annual cost of drugs for AIDS treatment often exceeded US\$10,000 per patient (A. S. Nunn et al., 2009; Outtersson, 2006). Demand for APIs to produce generics locally created economies of scale for generic ART. This in turn contributed to declining unit costs of generic ART, which, with new donor funding, contributed to developing countries' demand for generic ART, as well as APIs. This induced new generic firms to enter the ART market, increasing competition and further contributing to declining drug prices. India has emerged as a world leader in generic pharmaceuticals production, supplying 20% of the global market for

generic medicines. The emergence of generic sources supplying quality ART at prices much lower than originator prices has accelerated the global scale up of HIV/AIDS treatment. Price reductions noted for commonly used historical first-line regimens were a result of robust generic competition among Indian manufacturers in an environment largely void of intellectual property barriers (Ford et al., 2007). Since 2001, the pharmaceutical companies Roche, Gilead, Merck, Abbott, and Bristol-Myers Squibb have dropped their ART prices and introduced tiered pricing in many developing countries. Formerly a high-margin, low-volume model, the ART market has become a low-margin, high-volume model.

New intellectual property obligations for generic drugs can increase ART prices, impede the development of acceptable dosage forms, and delay access to newer and better HIV drugs. Such measures can undermine the international goal to achieve universal access to HIV/AIDS interventions and the 2001 WTO Doha Declaration on TRIPS and Public Health (World Health Organization, 2007). Arusha-based Tanzania Pharmaceutical Industry (TPI) has been producing ARVs but was suspended by the Tanzanian government in 2012 over manufacturing of fake ART (Rose Athumani, 2012). Under the World Trade Organization's trade-related aspects of intellectual property rights, poor countries like Tanzania are permitted to produce essential drugs without pharmaceutical product patents until 2016 (World Trade Organization, 2003).

1.3.1.3 Human resource, governance and training

The main limitation for ART scale-up in Tanzania is the low number and low productivity of clinical staff (Hanson et al., 2009). The shortage of staff limits both recruitment of new patients for ART and further reduction of the number of AIDS deaths. According to the 2009 Tanzanian care and treatment plan, CTCs should be located at hospitals and run by treatment teams of 18 staff members including 7 counsellors (UNITED REPUBLIC OF TANZANIA, 2003). Since the IMF-induced hiring freeze of government health staff in 1993, the total

number of health workers dropped from 67,000 in 1995 to 54,000 in 2002 and has been estimated to fall even further to 49,000 by 2015 (Kurowski et al., 2007). The IMF freeze was lifted after 11 years and the outputs from medical training institutions have increased (MOHSW, 2006), but many of these were recruited from within the workforce and as recruitment of new staff is a slow process (OECD/DAC, 2007) it will take several years before any real increase in staff numbers can be achieved. Responsible governance is crucial to national development and a catalyst for achieving the targeted treatment outcomes (Siddiqi et al., 2009). Governance seems a neglected issue in the field of human resources for health (HRH) but achieving attention in health systems (Dieleman et al., 2011) and thus why HRH policy formulation is poor. In Tanzania, it was found that decentralization of health services increased flexibility in planning and ownership of local services but also actually worsened distribution imbalances between areas in Tanzania rather than improving them (Munga et al., 2009). There is a shortage of HRH in Tanzania, low skill levels; most training is in-service, high staff rotation and inefficient distribution of staff the Tanzanian health sector (Wales et al., 2014).

1.3.2 Individual level issues

1.3.2.1 Adherence

Apart from AIDS, no other infectious disease has required lifelong therapy, and the challenges of equitable treatment of this chronic infectious disease are daunting; not the least among them is lifelong adherence to medications. Adherence is the single most modifiable factor that predicts treatment outcome among patients on ART. Adherence is defined as taking medications correctly according to prescription. According to recent studies, ART regimens require 70–90% adherence in order to be effective (Nachega et al., 2010). Rates of adherence in Africa have been reported as high as more than 90% (Amberbir et al., 2008; Coetzee et al., 2004; Oyugi et al., 2004) and a systematic review published in 2006 suggested that adherence, measured using quantitative indicators, was considerably better in Africa than

in the United States (Mills et al., 2006). In early treatment period characterized by a heavy viral burden, a higher adherence is required than the late treatment period when viral suppression is achieved (Carrieri et al., 2003). There are different methods for assessing adherence and the level of adherence is specific not only to places and patient groups but also to the method of adherence measurement used (R. J. Landovitz, 2011). Currently, there are no gold standard methods for measuring adherence (Nachega, Mills et al., 2010). Adherence measures include direct methods such as biologic markers and body fluid assays, or indirect methods such as self-report, caregiver report, interview, pill counts, pharmacy records, computerized medication caps, and viral load monitoring. While a combination of these methods may be employed, patient self-report is the most widely used (Vreeman et al., 2008a) given its ease of implementation and use of already existing resources. Studies have also indicated that self-reports correlate well with both viral load and clinical outcomes (Liu et al., 2001; Nieuwkerk et al., 2005). In developing countries, pharmacy refill reports and self-reports are commonly implemented for adults (Chesney, 2006; Nachega, Mills et al., 2010), while caregiver reports are employed for children. A number of studies have reported barriers to good adherence to antiretroviral therapy in the initial period after enrolment on to care, which have included: costs of visiting clinics to access care (Castro, 2005), which can be as high as 10-20% of monthly salary/wages per visit (Hardon et al., 2007; Jaffar et al., 2009), occurrence of unpleasant side effects, such as lipodystrophy (Chesney, 2000; M. O. Johnson et al., 2007) and HIV-associated stigma (Dlamini et al., 2009; Mahajan et al., 2008). Even people with typically excellent adherence will experience treatment interruptions owing to inevitable disruptions in daily routine, relapse of substance use or mental illness, or simple pill fatigue. Sub-optimal adherence can lead to periods of effective monotherapy (the presence of just one drug above the minimally effective concentration) when drugs have very different half-lives. Effective monotherapy is most likely to occur in patients on NNRTI-based treatments, because NNRTIs typically have longer half-lives than NRTIs (Bangsberg et al.,

2006). As such, adherence support may be necessary for many, if not most, people at some time in the course of life-long treatment in order to achieve the full individual and public health impact of antiretroviral therapy.

1.3.2.2 Loss to follow-up

The evidence continues to highlight the urgent need to improve retention rates for people enrolled in HIV care and treatment. Loss-to-follow-up (LTFU) (non-attendance at scheduled clinic visits) in HIV programmes in SSA is important among those eligible for ART, given the risk of mortality and morbidity, onward transmission and ART resistance with inconsistent medication use (Cornell et al., 2010). High levels of attrition from HIV programmes in SSA have been reported in the period between the assessment of individuals as ART eligible and treatment initiation (Rosen et al., 2011). For those who have started ART, attrition rates of 23% at one year, 25% at two years and 30% at three years in SSA have been estimated (Fox et al., 2010). A number of clinical, demographic and structural factors have been shown to relate to higher rates of LTFU in individuals on ART (or those eligible to start ART) in SSA. Clinical correlates of higher LTFU include both lower (Togun et al., 2011), and higher CD4 count (Mutevedzi et al., 2013; Van Cutsem et al., 2011), poorer adherence to ART (Karcher et al., 2007) and TB co-infection (Bassett et al., 2012; Tayler-Smith et al., 2011). Demographic correlates of LTFU include male gender (Charurat et al., 2010; Karcher, Omondi et al., 2007), younger age (Cornell, Grimsrud et al., 2010; Van Cutsem, Ford et al., 2011; Wang et al., 2011), pregnancy for women (Wang, Losina et al., 2011), lower levels of education (Charurat, Oyegunle et al., 2010), financial constraints (Cornell et al., 2009), and migration (Mutevedzi, Lessells et al., 2013), (Bygrave et al., 2010). Structural correlates include less distance to a tarred road (Mutevedzi, Lessells et al., 2013), later calendar year of ART initiation (Van Cutsem, Ford et al., 2011) and increased time on ART (Van Cutsem, Ford et al., 2011). Nearly half of all people who initiated antiretroviral therapy at the same

treatment centre in Malawi were no longer in care five years later, and this proportion was nearly 40% in Kenya (UNAIDS, 2012c). A study conducted in four countries SSA found that community supported models of care for people on HIV treatment improved retention; reduced indirect medical cost (travel and lost income) and the number of clinical visits (Bemelmans et al., 2014). A meta-analysis covering 13 African countries suggests that 40% of all ART clients might have died or discontinued treatment within 2 years after treatment initiation (Rosen et al., 2007). The attrition rate of patients from care and treatment programmes in Tanzania is high, highlighting the need for concerted efforts to improve tracing mechanisms to document the true outcomes for these patients and to encourage them to return to care in the case of default (NACP, 2013b).

1.3.3 ART outcome

1.3.3.1 Virological failure

Virological failure is the inability to achieve or maintain viral suppression to an HIV RNA level below detectable limits. It is generally believed that drug resistance associated mutations do not occur in patients with HIV RNA levels persistently suppressed to below the lower limits of detection (LLOD) of recent assays (Kieffer et al., 2004). After ART initiation, most patients experience improved immune function and maintain viral suppression; however, there remains a subset of patients who have suboptimal immunologic responses. In ART-naive patients on initial regimens, during the first year of ART initiation, CD4 counts usually increase by approximately 150 cells/mm³ (Bartlett et al., 2001). A CD4 count plateau may occur after 4 to 6 years of treatment with suppressed viremia (F. Garcia et al., 2004; Kaufmann et al., 2003; Lau et al., 2007; Mocroft et al., 2006; Moore et al., 2007; Tarwater et al., 2001). Studies have attributed treatment failure to previous ART exposure, non-adherence or treatment interruptions and drug resistance. A study done in Tanzania and South Africa showed an increased risk of virologic failure in previously ART exposed HIV positive

patients (El-Khatib et al., 2011; Ramadhani et al., 2007). The trend is similar when children are exposed to single-dose nevirapine in prevention of mother-to-child transmission (PMTCT) (Stringer et al., 2010). A cross-sectional relationship between adherence and virologic suppression has been demonstrated in Brazil (R. Garcia et al., 2006) and a sub-optimal ART was associated with lower virologic success in Cambodia (Segeal et al., 2011). Treatment interruptions are associated with the development of ARV resistance (Bansi et al., 2008; Martinez-Picado et al., 2002; Oyugi et al., 2007; Parienti et al., 2004). Treatment failure needs to be detected early enough to minimize the effect it has on increased morbidity and mortality among patients on ART. Possible solutions to treatment failure include appropriate switch to second-line regimen or further adherence support (Abrams et al., 2013).

1.3.3.2 Drug resistance

Antiretroviral drug resistance is a result of substitution of some amino acids in the HIV Reverse Transcriptase (RT) and protease enzymes. The intra-patient viral population is a highly dynamic system, characterized by a high turnover and high mutation rate (Domingo et al., 1997; M. Nowak et al., 2000). HIV-1 replicates at a high rate in untreated patients, with at least 10^{10} new virions produced and cleared per day (Perelson et al., 1996). HIV-1 reverse transcriptase lacks proof-reading capability, so the mutation rate is high (1 in 10^4 to 1 in 10^5 nucleotide mutations per replication cycle, or about one mutation per newly produced viral genome) (Coffin, 1995; Mansky et al., 1995). This ability of HIV-1 to adapt to potent drug pressure was clearly shown in the studies of nevirapine and maternal-fetal transmission; a single dose of nevirapine given at the time of delivery was sufficient to select for a dominant virus population with genotypic drug resistance (Jackson et al., 2000). The virus population present at a certain time point within an infected individual consists of a complex mixture of heterogeneous strains (quasispecies) (Meyerhans et al., 1989). The quasispecies continuously compete among themselves and for survival and propagation (Fisher et al., 1988). The

subsequent overgrowth or dominance of a certain viral strain over another is largely determined by its relative adoption to its intra-host environment, a factor particularly relevant to the emergence of drug resistance virus variants. These evolutionary dynamics are the basis for a diversified population that can quickly generate drug resistance variants in response to the therapy (Metzner et al., 2013; M. A. Nowak et al., 1997). If viral mutations are associated with HIV drug resistance, these viral variants can have selective advantage and avoid drug pressure (Ho et al., 1995; Preston et al., 1988; Wei et al., 1995). Several studies have shown that low adherence is associated with increased risk of resistance emergence (Bangsberg et al., 2003; Harrigan et al., 2005; Parienti, Massari et al., 2004; Sethi AK et al., 2003). Treatment interruptions of 2 or more days predicted resistance mutations in Uganda (Oyugi, Byakika-Tusiime et al., 2007). In 2013, a study in South Africa showed that 6% of patients had a least one drug resistance mutation.

Transmitted drug resistance does not result only from transmission after therapy failure in chronic patients but can be driven by on-going transmissions, if the resistant strain is fit enough for transmission and if the mutation(s) persists in the absence of drugs (Frange et al., 2012; Yerly et al., 2009). A transmitted virus which harbours the K103N mutation, is able to persist without drug pressure (Gianotti et al., 2005) and K103N which is associated with resistance to Efavirenz and Nevirapine, two drugs that are widely used and recommended in first-line therapies.

HIV-1 mutations associated with drug resistance are classified as either primary (major) or secondary (minor). Primary mutations are selected under drug pressure, may lead to a decrease in sensitivity to one or more antiretroviral drugs, and are extremely rare in the absence of treatment (Hirsch et al., 1998). Secondary mutations are defined as having little or no effect on drug susceptibility, but may lead to increased resistance or increased replication capacity in the presence of major mutations (Erickson et al., 1999; Hirsch, Conway et al., 1998). The prevalence of HIVDR among ART-naive people in the USA and Europe has been

estimated to be 10%-15% (Simen et al., 2009; Wittkop et al., 2011). In SSA, HIVDR was reported to be less than 5%, with growing evidence of increasing levels of resistance (Hamers et al., 2010; Manasa et al., 2012; Price et al., 2011). Studies in SSA demonstrated that the prevalence of resistance associated mutations (RAMs) in patients failing first-line ART ranged from 53 to 84% with 38 to 64% harboring dual-class resistance (Hamers et al., 2012; Hassan et al., 2014; Liegeois et al., 2012; Marconi et al., 2008).

The International AIDS Society USA guidelines for the use of ART in adults recommend testing for HIVDR prior to initiation of therapy in high-resources countries (Hirsch et al., 2008; Thompson et al., 2010). The WHO global HIVDR prevention and assessment strategy (Bennett, Bertagnolio, et al., 2008), which includes laboratory-based surveys of acquired (Jordan et al., 2008) and transmitted (Bennett, Myatt, et al., 2008) HIVDR, monitors HIVDR Early Warning Indicators (EWI). EWI assess ART site and program factors potentially associated with HIVDR (WHO, 2010e). Utilizing data routinely collected in patients' medical and pharmacy records, EWI monitoring is a minimum-resource strategy designed to be integrated into national monitoring and evaluation programs. EWIs survey factors related to patient care, patient behavior, and clinic-level and program management, all of which are associated with the emergence of HIVDR. When monitored annually at all or a large number of representative ART sites, EWIs provide countries with evidence to make programmatic adjustments at the level of an individual site or the country, when necessary. WHO updated their EWI definitions in 2012 (WHO, 2012). The baseline prevalence of HIV drug resistance in Kilimanjaro-Tanzania among HIV risk group (sex workers and bar maids) was estimated to be 7% (Kiwelu et al., 2014). Another study among HIV patients not eligible for ART initiation in Mwanza – Tanzania found the prevalence of RAM was around 18.2% (Kasang, Kalluvya et al., 2011). A study on patients eligible for ART initiation done in Kilombero Tanzania, found the prevalence to be 8.4% (Masimba et al., 2013).

1.5 HIV/AIDS management in Tanzania

1.5.1 Tanzania National Aids control programme (NACP)

The National AIDS control program (NACP) was established in 1987 under Ministry of health and social welfare with the overall aim of reducing incidence of HIV infection and its associated morbidity and mortality (TACAIDS, 2009a). The HIV/AIDS care and treatment plan was launched in October 2004 with the aim of providing quality care and treatment to all HIV infected patients in Tanzania. Access to ART has increased after then from 0.5% (NACP, 2013a) in 2004 to 65% in 2013 (NACP, 2013b) of patients in need. Patients with a CD4 count <350 cells/ μ l of whole blood, on WHO stage IV regardless of CD4 count and pregnant women with WHO stage III or IV regardless of CD4 + T cell count were eligible to start ART. Due to limited resources, a public health approach where by CD4 and WHO clinical staging are used to monitor HIV positive patients. The funding for the ART management in Tanzania is largely donor supported (95%) and major funding comes from the Global Fund for AIDS, TB and Malaria and the United States President's Emergency Plan for AIDS Relief (PEPFAR) which contribute two thirds of the total donation (TACAIDS, 2008, February).

1.5.2 Chronic Disease Clinic Ifakara (CDCI)

The Chronic Diseases Ifakara (CDCI) started providing HIV care and treatment in Ifakara in 2005. The observational open HIV cohort Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) is managed and supervised by the Ifakara Health Institute (IHI) and the adjacent Saint Francis Referral Hospital (SFRH) (Mossdorf et al., 2011; Mossdorf et al., 2010; Stoeckle et al., 2006). Since its opening, the CDCI has enrolled 6,500 HIV-positive clients, 3600 of which initiated ART as of July 2012. SFRH (formerly SFDDH) was the first rural District Hospital in Tanzania accredited by the National AIDS Control Programme to

become a Care and Treatment Centre at the end of 2004. Since then, uninterrupted VCT services and comprehensive care for an increasing number of persons living with HIV/AIDS have been offered at Ifakara (Stoeckle, McHomvu et al., 2006). During the study period, all patients with CD4 count <350 cells/ μ l of whole blood, patients with WHO stage IV regardless of CD4 count, and pregnant women with WHO stage III or IV regardless of CD4 count were eligible to start ART (NACP, 2008a; WHO, 2010b). Additionally, patients are required to come to the clinic with an adherence assistant who will help them to take their ART correctly. The patient has to visit the clinic on scheduled appointment or any time he/she feels a need to do so.

2.0 CHAPTER TWO: Rationale, objectives and goals

2.1 Rationale

There is a rapid scale up of ART for individuals with HIV in the developing world. The adoption of the public health guidelines to enhance ART programmes in Africa has led to treatment outcomes comparable to those attained in the Northern America and West Europe (Braitstein et al., 2006). The challenges observed in resource poor settings are access to ART, adherence issues and resistance associated mutations (RAM). All these factors limit the effectiveness of ART programs. There is a need to understand these parameters in Tanzania especially at a time when ART is being largely scaled up in rural settings. With this knowledge, the ministry of health and social welfare (MOHSW) may design appropriate strategies to reduce HIV associated morbidity, death and its associated cost to the health system. Being among one of the first CTCs to be introduced at the district level, serving two districts and caring and treating more than 6000 patients, the CDCI offers an excellent opportunity to address gaps in knowledge on supply management of ART, adherence to ART in rural TZ as well as risk factors associated with drug resistance.

2.2 Goal

The goal of the study was to study supply of drugs, adherence patterns and drug resistance mutations so as to propose appropriate actions to improve the ART management in rural Tanzania.

2.3 Objectives

2.3.1. Main objectives

1. Assessing the supply chain management for HIV/AIDS treatment in Kilombero and Ulanga districts.
2. Study adherence levels of children and adolescents
3. Identify the predictors of adherence among patients attending the CDCI
4. Investigate factors associated with drug resistance associated mutations

2.3.2. Specific objectives

- i. Assess the supply chain of HIV test kits and drugs in Kilombero and Ulanga CTCs
- ii. Evaluate key aspects of patient management such as functioning of laboratory services, initiation and modification of ARTs and resources spent by patients' to access care in rural settings.
- iii. Describe the coping strategies of the CTCs and ART patients in times of stock-outs of HIV test kits, cotrimoxazole and ART.
- iv. Investigate determinants for ART adherence and explore barriers and facilitators of adherence among children and teenagers in rural Tanzania.
- v. Investigate the determinants of adherence among patients on ART attending CDCI.
- vi. Investigate risk factors for ART resistance mutations among patients attending CDCI

CHAPTER THREE: An assessment of supply chain management for HIV care in Kilombero and Ulanga districts

ABSTRACT

Background

The Chronic Diseases Clinic Ifakara (CDCI) has been providing HIV care and treatment in Ifakara since 2005. Over time, several drug-refilling stations were created through the Tanzanian National AIDS Control Programme (NACP) to provide antiretroviral therapy (ART). Without any specific performance and outcome evaluation, these refilling stations were upgraded to comprehensive HIV care and treatment centres (CTCs). The objectives of this study were to evaluate the supply chain of the CTCs; key aspects of patient management and the coping strategies of the CTC staff and ART patients during stock-outs of drugs and test kits.

Methodology

In this cross sectional study, data were collected through structured interviews with staff in charge of 12 sites and patients on ART during un-announced visits. Data was analysed using STATA 11.0. Hypotheses were tested using χ^2 -test for categorical variables and Mann-Whitney U test for continuous data.

Results

All sites reported rapid test shortages to diagnose HIV. Seven CTCs (59%) experienced stock-outs of cotrimoxazole drugs. The CDCI and all but one peripheral CTC reported stock-outs of ARV medication. CD4 + T cell count service and second line drugs were available at the CDCI and in two CTCs only. To cope with the stock-out situation CTCs staff had to stop testing for HIV, substitute the regimen depending on drug availability or closed the CTC temporarily. Patients coped by skipping ARVs and cotrimoxazole medications.

Conclusion and recommendations

Access to ART in Kilombero and Ulanga districts has some critical imbalances in the supply chain and management for HIV/AIDS care and treatment. Strategies to overcome the barriers are: (i) Routine data collection on ART supplies to estimate actual demand, (ii) Investments into mobile-health (m-health) for minimizing stock-outs problems, and (iii) more ART management training to be done on peripheral CTCs staff.

BACKGROUND

Care and Treatment Centres (CTCs) to provide care and treatment to HIV patients were introduced in Tanzania through the National AIDS Control Program (NACP) in 2003 (UNITED REPUBLIC OF TANZANIA, 2003). The NACP is integrated into the Tanzanian health care delivery system and HIV/AIDS care and treatment is based at the primary, secondary and tertiary referral levels (district, region, referral hospitals) (UNITED REPUBLIC OF TANZANIA, 2003). The Clinic for Chronic Diseases Ifakara (CDCI) in Kilombero district, was one of the first CTC to be established in Tanzania, and started providing ART since 2005 (Stoeckle, McHomvu et al., 2006). The CDCI is managed and supervised by the Ifakara Health Institute and Saint Francis Referral Hospital. Since its opening, the CDCI has enrolled 6,500 HIV-positive clients, 3600 of which initiated ART as of July 2012.

The Voluntary Counselling and Testing (VCT) unit of the CDCI and CTCs routinely offered sequential rapid diagnostic tests (Mossdorf, Stoeckle et al., 2011) to establish HIV serostatus. As part of the efforts to decentralize HIV/AIDS care and treatment and to make antiretroviral therapy (ART) more accessible, several district level drug refilling sites were established in 2009 through the NACP (TACAIDS, 2008). These drug refilling stations were originally designed to provide antiretrovirals in the periphery and refer critical patients to the next CTC available for further management, but were not entitled to initiate or modify ART. After two years and without any specific performance and outcome evaluation, they were upgraded to full CTCs. The upgrade from refilling stations to CTCs aimed at improving services and access to HIV patients and thus providing comprehensive care for patients at peripheral settings. These include ART initiation, treatment change and handling of more complex issues in HIV patient's management. These changes were expected to save patient's time and resources while improving the quality of care and patients' quality of life.

Thus, the original refilling stations are now operating as peripheral CTCs linked to the large ART-cohort at the CDCI. The CDCI has been supervising the former drug refilling stations in Kilombero and Ulanga districts from the beginning of their activities based on the NACP guidelines.

The present study was undertaken to evaluate the overall situation of ART service delivery in the Kilombero and Ulanga districts within the context of central CDCI and upgraded refilling stations. The specific objectives were to (i) assess the supply chain of the CTCs, (ii) evaluate key aspects of patient management such as functioning of laboratory services, ART management and resources used by patients to gain access ART (iii) describe the coping

strategies of the CTCs and ART patients in times of stock-outs of HIV test kits, cotrimoxazole and ART.

MATERIALS AND METHODS

Study design, settings and participants

This explorative and cross-sectional study was undertaken in September 2011 and involved CDCI and all 11 peripheral CTCs in Kilombero and Ulanga districts. The peripheral CTCs were in Lupiro, Mahenge, Mwaya, Mtimbira, Lugala, Itete, Mngeta, Mlimba, Kibaoni, Mang'ula and Ilovo as shown in Figure 1. Kilombero district is mainly a river plain with fertile alluvial soil while Ulanga is mountainous with some low-lying areas. The main economic activities of the population are subsistence farming and fishing (Masanja et al., 2006).

The study targeted the person in charge of the facility (CTCs or CDCI) and adult ART patients attending the CTCs/CDCI on the date of study visit or who attended recently in the case that no ART patients attended the clinic on study visit date. We interviewed every second patient to reduce selection bias as family members tend to attend clinic at the same time. Critically ill patients as determined by the respective physicians were excluded from the study.

Data collection

Semi-structured questionnaires were designed and piloted in two CTCs (Kibaoni and Mang'ula) and at the CDCI. Field interviewers were recruited, specifically trained and supervised during the entire data collection period.

Interviews with person in charge of CTC aimed at establishing (i) the overall functioning of the CTC; (ii) the occurrence of stock-outs of HIV rapid test kits; (iii) possible coping strategies of health staff and clients during stock-outs of HIV rapid test kits; (iv) whether medicines were delivered in time; (v) the frequency, determinants and dynamics of ART

supplies and necessary drug changes and (vi) stock-outs experiences in the year preceding the study. In case of incomplete information, we visited respective sites up to three times to get the missing data. When ART patients were unavailable at the clinic, we had to visit them at their home with the help of a CTC staff.

The patient interview included the following variables: place of residence, facility where CD4 + T cell count was analysed for the last time before ART initiation, changes in ART regime and the treatment centre where the changes took place, reasons for the changes, duration under ART, whether they ever stopped medication and transport and accommodation costs associated with treatment (cost information was collected in Tanzania shillings and later converted to US dollars at an exchange rate of 1600 TSH per dollar; rates September 2011).

Data analysis

Data were double-entered using EPI-DATA (EpiData Association, Odense, Denmark) and analysed using STATA 11.0 (STATA Corp., College Station, Texas, USA). The Shapiro-Wilk test was used to test for normality. Statistical tools for hypothesis testing were χ^2 -test for categorical variables and Mann-Whitney U test for continuous variables that followed a non-normal distribution.

Ethical considerations

The study was undertaken as part of the Kilombero and Ulanga Antiretroviral Cohort project (Mossdorf, Stoeckle et al., 2011) that received ethical and research clearance from the Ifakara Health Institute Institutional Review Board and the Medical Research Coordinating Committee of the National Institute for Medical Research. Research permit was granted by the Tanzania Commission for Science and Technology. All study participants provided oral informed consents.

RESULTS

We managed to visit 11 CTCs and the CDCI for the interviews. The 11 CTCs in Kilombero and Ulanga districts were located between five and 150 kilometers from the CDCI. At the time of the study, the CTCs served between 48 to 700 HIV positive patients each.

Participant's characteristics

A total of 89 ART patients (25 at CDCI and 64 at CTCs) were involved in the study (Table 1). In addition, 12 health care providers who were in charge of the CTCs and the CDCI were interviewed. At the CDCI the person in charge was a medical doctor and at the CTCs, five clinical officers and six nurses/midwives/assistant medical officers were included. All CTC staff, including those interviewed, had attended specific training for HIV care and treatment.

Supply chain management of HIV test kits, cotrimoxazole and ART

All responsible persons of the CTCs or CDCI interviewed reported to have experienced stock-outs of rapid tests to diagnose HIV in the year preceding the study. CDCI and three CTCs experienced stock-outs of HIV test kits only once, five CTCs (42%) experienced stock-outs at least twice while three CTCs (25%) did not know how often stock-outs happened. The stock-outs lasted for an average of 5.6 weeks (range: 1 week - 3 months). At the time of the survey, CDCI had both HIV diagnostic tests in stock while 5 (42%) and 3 (25%) CTCs did not have Bioline or Determine, respectively. An additional 3 CTCs (2 in Ulanga district) did not have any tests available at the time of the survey. The CDCI and 2 peripheral CTCs reported to get HIV test kits on time when ordered during stock-outs period, 7 of the CTCs reported that it took two or more weeks, 1 reported that it took 3 months to receive the HIV test kits once they were out of stock.

CDCI and 36% (4/11) of the CTCs reported to have never experienced stock-outs of cotrimoxazole in the year preceding the study. Six patients (9.3%) at peripheral CTCs reported to have not taken cotrimoxazole tablets because of stock-outs. Among the patients who reported stock-outs of cotrimoxazole drugs in the peripheral CTCs, three of them experienced this once, two of them twice and one experienced stock-outs more than twice. Of

these six, three of the patients reported that the stock-outs lasted for more than one month; one patient reported that it lasted for one month and 2 patients reported the stock-outs lasted for one day. In the year preceding the study, CDCI and 91% (10/11) of the peripheral CTCs reported to have experienced ARV stock-outs in the past year. The only site that never experienced insufficient supplies was the Kibaoni CTC at the administrative centre of the Kilombero district. Two out of 64 patients reported to miss their ARVs, one because of stock-outs at the nearest CTC and the other person ran out of pills.

The CDCI and 36% (4/11) of the peripheral CTCs reported not to receive drugs in time in the year preceding the study due to delays in delivering after an order was posted. The peripheral CTCs mentioned that (i) there was no one responsible for ordering at the clinic (ii) they were late in ordering drugs (iii) there was a poor transport chain or (v) there were no drugs at the distributor's site.

Key aspects of patient's management

Functioning of laboratory services (point of care CD4 services)

During the study period, CD4+ T cell count analysis was only processed at the CDCI and in 2 CTCs (Mahenge and Lugala). In the Kilombero district, patients from other CTCs had to travel to CDCI for CD4+ counts. In contrast, blood samples of patients in Ulanga district were brought to Mahenge and Lugala CTCs or CDCI for the CD4 + T cell count analysis.

Drug (ARV) management

Among 20 patients interviewed at the CTCs who reported to have changed their ART regimen, 17 (85%) of them had their drug modified at the CDCI while drug modifications of the remaining 3 (15%) were done at the CTCs. All patients who were interviewed at the CDCI reported to have had that their drugs modified at the CDCI. Forty percent of peripheral CTCs patients whose drugs were modified came from just three CTCs (Mahenge, Mlimba and Mngeta). Staff in charge of one CTC reported to have stopped ARV medication in a patient with multiple organ failures (kidney and liver failure).

According to patients at the peripheral CTCs, the main reasons for modifying ARV regimens were side effects (70%), stock-outs (15%), clinical decisions (10%) and pregnancy (5%). The main reasons stated by the health worker in charge of the CTCs were side effects (82%), pregnancy and co-infection with tuberculosis and other diseases (63%), stock-outs (45%) and clinical decisions (18%) (Multiple answers were common). Two patients at CTCs (3%) reported to have decided on their own to stop their medication in the past because of side effects. None of the patients interviewed at CDCI/CTCs was ever recommended to stop the ART drugs for any reasons by an ART clinician.

Personal expenditures associated with ART

Although care and treatment of ART patients are free of charge, there are costs associated with the treatment, particularly for transport and accommodation when having to visit CDCI or CTCs. There were significant differences in costs incurred between seeking health care in CTCs and CDCI. Visiting a peripheral CTC costed US\$ 8.7 less on transport and US\$ 5.3 less on accommodation. It took three hours less to reach the CTC than the CDCI as shown in Table 2.

Coping strategies

The CTCs, CDCI and patients had adopted several strategies to cope with stock-outs of HIV test kits and medicines. Apart from stopping HIV tests, they also changed the drug regimen while still maintaining triple therapy, temporarily closed the CTC and suspended taking medication. One and six patients stopped taking ARVs and cotrimoxazole, respectively after they were told of stock-outs during their clinical visits. The CDCI and 7 peripheral CTCs (64%) reported to have stopped HIV testing when they were out of stock of test kits, 2 CTCs (17%) reported to post orders, while 1 (8%) reported the information to local authorities to inform them about the situation. Staff in charge of one CTC did not know what was done after the stock-outs.

In case of stock-outs of ARV drugs at the CDCI, communication was made with the nearest CTC (Kibaoni) for locally of sharing of ARVs treatment is changed while still maintaining triple therapy. In the peripheral CTCs, patients were referred to another CTC (if on second line, the patients were referred to CDCI), or they were told to come back when drugs were available or changed to alternative regimens within the first line while maintaining the triple therapy. One CTC reported to shut down the CTC office during the period of stock-outs.

DISCUSSION

This cross-sectional study done in Kilombero and Ulanga has found stock-outs of HIV test kits and ARVs is common. There is also a limited access of second line and CD4 point of care machine and coping strategies that actually create additional problems.

Because knowledge of one's HIV status is the entry point for all HIV care and treatment services, stock-outs of HIV testing kits have major impact on the effectiveness of the HIV control program particularly with respect to access to and retention in care. All sites visited had experienced stock-outs of HIV test kits in the year preceding the study. There was a countrywide (Tanzania) stock-out of HIV test kits for several months in 2011. An assessment of lower level health facilities in Tanzania preceding the introduction of HIV/AIDS care and treatment reported that more than 90% of facilities did not have adequate laboratory supply chains for laboratory materials (NACP, 2009). The main goals of programmes aiming at reducing HIV incidence may not be achieved as long as stock-outs of HIV test kits prevail. Stock-out of test kits and drugs has been reported to also affect other HIV programmes including Prevention of Mother to Child Transmission (Aavitsland et al., 2002; Gamell et al., 2013), HIV screening for blood transfusion and VCT. As more people remain unaware of their serostatus because of lack of HIV tests, there will be an increased risk of infecting other individuals with the deadly virus (Hall et al., 2012). Careful monitoring, surveillance and comparative analyses will reveal to what extent stock-outs impact global HIV dynamics.

Stock-out of cotrimoxazole was common in the study area. WHO recommends provision of co-trimoxazole prophylaxis as long as CD4 cell count <350cells/ml, during pregnancy and in children born to HIV positive mothers (NACP, 2008b). Cotrimoxazole is a highly cost-effective approach to reduce mortality among patients who present with advanced HIV at ART initiation and it also yields benefits for people with opportunistic infection (Abimbola et al., 2012). Randomized trials that included ART-naive Africans found that cotrimoxazole improved survival while reducing the risk of malaria, pneumonia, sepsis, isosporiasis, toxoplasmosis encephalitis and wasting (Anglaret et al., 1999; A. J. Nunn et al., 2008; Wiktor et al., 1999). Stock-outs of the drug, resulting in a higher number of HIV patients developing opportunistic infections (Sethi et al., 2003), may further accelerate HIV disease progression (Nischal et al., 2005), increase hospital admissions (Mulenga et al., 2007) and increase both health care costs (McDonnell et al., 2002) and mortality rates (Wood et al., 2003) among HIV patients.

All but one peripheral CTCs experienced stock-outs of ART drugs. In many low- and middle-income countries, the capacity of the procurement and supply management systems has always been weak (Pasquet et al., 2010). A WHO survey in 2009 revealed that 38% of countries had documented at least one stock-out of antiretroviral (ARV) drugs in health facilities (WHO, 2010d). Stock-outs of ARVs directly affect adherence to antiretroviral therapy (Weidle et al., 2006) which in turn increases the risks of resistance development, disease progression (Oyugi, Byakika-Tusiime et al., 2007) and mortality (Garcia de Olalla et al., 2002). A study conducted in northern Tanzania revealed that stock-outs led to no/few drugs being dispensed to HIV patients (Lyimo et al., 2012). Stock-outs of ARVs for the PMTCT programme mirror the general health system inadequacies within which the PMTCT programmes are implemented as reported in other African countries (Nkonki et al., 2007). Interestingly, a report of NACP preceding care and treatment scale up found that only one

third of 553 lower level health facilities had a tracking system for ARVs in place and has sufficient storage space for a one month stock of ARVs (NACP, 2009).

Patients from the three sites (Mlimba Mngeta and Mahenge) had a higher proportion of drug changes which might have been attributed by the long distance from the supply site and thus have drug delays and shortages, hence are forced to send their patients to CDCI where changes are prescribed. A decrease in ART coverage has been associated with a proportional increase in HIV incidence among HIV uninfected adults (Hontelez et al., 2013). With the stock-outs of ART, fewer people will be under ART and we should expect a relatively higher HIV incidence among uninfected people.

Some coping mechanism adopted by the sites studied appeared to create additional problems. Closing temporarily the CTC might discourage clients from testing and thus increase the proportion of HIV positive people who are not aware of their status. A study conducted in Iringa region showed that some clients gave up testing completely after being turned away after stock-outs of HIV test kits, (Layer et al., 2014). A study in Zimbabwe revealed priorities were focused on PMTCT during times of HIV stock-outs (Kranzer et al., 2014). In some settings to cope with stock-outs, staff did dispense few pills so that many ART patients can get at least some (Lyimo et al., 2011). This option should be discouraged as it will likely lead to ART resistance mutations and treatment failure (Clavel & Hance, 2004; Tang et al., 2012). CD4 + T cell count analysis was done in very few sites in Kilombero and Ulanga districts. The reasons besides costs include a lack of skilled laboratory staff; the inability to maintain machines and/or assure reliable data; difficulties in managing the supply of reagents and a lack of adequate quality assurance schemes to ensure reliable results (Birx et al., 2009). Absence of point of care CD4 + T cell count may delay staging of HIV patients on site and thus increases the possibility of loss to follow-up (Jani et al., 2011).

Our study had several limitations. Firstly, the study had to rely on estimates of the staff in charge of the CTCs if the information required was not documented or unavailable. Secondly,

the study had also a small number of ART patients and thirdly, and we did not ask follow-up questions such as on how many patients who were referred to another CTC for drugs actually went there. Nevertheless, our study has several strengths. The survey was unannounced, patients were randomly selected and staffs in charge of the CTCs in the region and the CDCI were included. Based on the fact that all CTCs in Tanzania have the same source of drug, we are confident that the study possessed internal validity and can be generalized to reflect situation in other peripheral CTCs in Tanzania and in other resource limited countries.

In conclusion, access to ART in Kilombero and Ulanga districts has some critical imbalances in the supply chain and management for HIV/AIDS care and treatment. Potential strategies to overcome these barriers and improve the functioning of CTCs in harmonization with the central CDCI should be considered by the NACP and the district health teams. Our study suggests the following: (i) Routine data collection on HIV test kits and drugs supplies to estimate the actual demand and early ordering of the items, (ii) Investments into mobile-health (m-health) by a targeted use of mobile phones for supervision and reducing stock-out problems in analogy to “SMS-for-life” in malaria (World-Bank) and (iii) more ART management training to be done on peripheral CTCs staff with special emphasis on how to handle second line drugs and complicated cases at their sites.

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Competing interests

The authors declare that they have no competing interest.

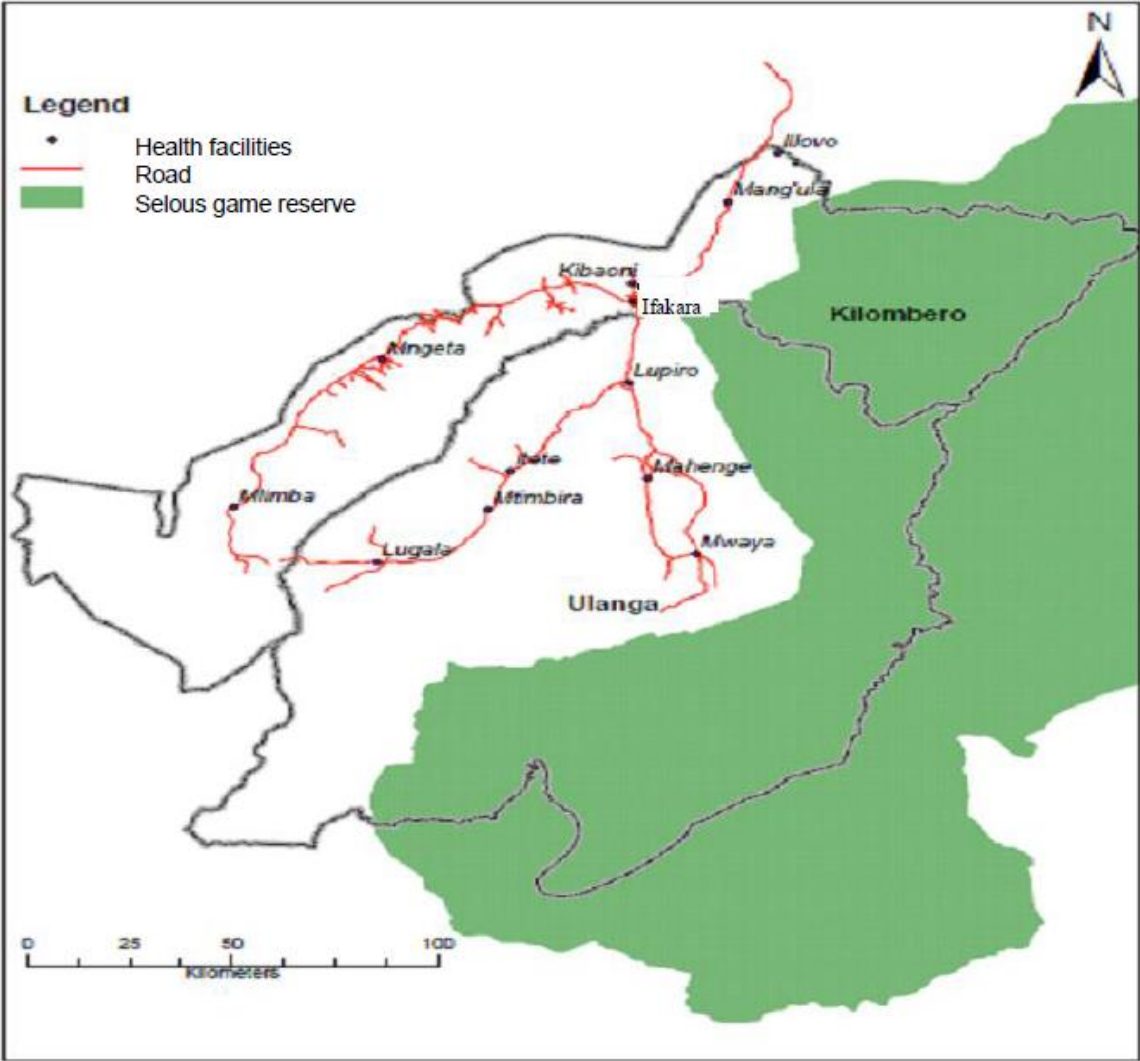
Table 1 Participants characteristics

	CTCs		CDCI	
	n	%	n	%
No of patients	64	72	25	28
Sex				
Male	21	32	13	54
Female	43	68	12	46
District				
Kilombero	35	55	23	92
Ulanga	29	45	2	8
Where CD4 analysed before ART initiation				
CDCI	31	48	21	84
Others	33	52	4	16
Incurred transport cost				
Yes	26	41	16	64
No	38	59	9	36
Incurred accommodation cost				
Yes	1	2	20	80
No	63	98	5	20
Duration on ART in yrs (mean)	1.8 (1.3-3.2)		2.2 (1.1-3.3)	
CTC: Care and treatment centres at peripherals, CDCI: Chronic Diseases Centre Ifakara, yrs: years				

Table 2: A table showing resources used to get access to the CDCI and CTCs

	CTC	CDCI	P-Values
	Median (IQR) N	Median (IQR) N	
Transport cost (US \$)	1.3, (0.6-1.9), 26	10, (6.3-12.5), 15	<0.001
Accommodation cost* (US \$)	1	6.3, (1.9-6.9), 20	NA
Travel time (hours)	1, (0.5-2), 42	4, (3-5), 23	<0.001
<p>*P-value for accommodation cost could not be calculated as there was no standard deviation because only one patient had incurred accommodation cost while attending peripheral CTC. Transport cost included go and return fares from home to CTCs. Cost were collected in Tanzanian shilling and later transformed to US \$</p>			

Figure 1 Map of Kilombero and Ulanga showing CDCI and CTCs



NB; There are 6 CTCs (including CDCI) in Kilombero district and 6 CTCs in Ulanga district

CHAPTER FOUR: ART adherence to HIV positive children and adolescents

ABSTRACT

Background

Around 3.3 million children worldwide are infected with HIV and 90% of them live in sub-Saharan Africa. Our study aimed to estimate adherence levels and find the determinants, facilitators and barriers of ART adherence among children and teenagers in rural Tanzania.

Methods

We applied a sequential explanatory mixed method design targeting children and teenagers aged 2-19 years residing in Ifakara. We conducted a quantitative cross sectional study followed by a qualitative study combining focus group discussions (FGDs) and in-depth interviews (IDIs). We used pill count to measure adherence and defined optimal adherence as $\geq 80\%$ of pills being taken. We analysed determinants of poor adherence using logistic regression. We held eight FGDs with adolescent boys and girls on ART and with caretakers. We further explored issues emerging in the FGDs in four in-depth interviews with patients and health workers. Qualitative data was analysed using thematic content analysis.

Results

Out of 116 participants available for quantitative analysis, 70% had optimal adherence levels and the average adherence level was 84%. Living with a non-parent caretaker predicted poor adherence status. From the qualitative component, unfavorable school environment, timing of the morning ART dose, treatment longevity, being unaware of HIV status, non-parental (biological) care, preference for traditional medicine (herbs) and forgetfulness were seen to be barriers for optimal adherence.

Conclusion and implications

The study has highlighted specific challenges in ART adherence faced by children and teenagers. Having a biological parent as a caretaker remains a key determinant of adherence among children and teenagers. To achieve optimal adherence, strategies targeting the caretakers, the school environment, and the health system need to be designed.

BACKGROUND

At the end of 2012, an estimated 35.3 million [32.2–38.8 million] people were living with HIV. The UNAIDS global report 3.3 million children had HIV globally, 2.9 million in sub-Saharan Africa (UNAIDS, 2013c). In 2012, there were 230,000 children living with HIV and 1.3 million orphaned by AIDS in Tanzania (UNAIDS, 2012c). Treatment of HIV infected patients with ART has resulted in a dramatic reduction in HIV related morbidity and mortality (WHO/UNAIDS/UNICEF, 2011). Successful treatment results in virological suppression, an increase in the CD4+ T cells count, and improvement in the clinical well-being of the individual, manifesting as weight gain and resolution or control of opportunistic infections (Paintsil, 2011). Adherence to treatment regimens is a prerequisite for the efficacy and durability of any ART (Harries et al., 2004; Paterson et al., 2000). According to recent studies, ART regimens require 70–90% adherence in order to be effective (Nachega, Mills et al., 2010). Some studies show that viral suppression for patients treated with non-nucleoside reverse transcriptase inhibitors (NNRTI) is possible with adherence levels ranging from 54%–100% (Bangsberg, 2006). Poor adherence to ART regimens results in incomplete suppression of HIV replication and emergence of resistance to ART that increase the potential for treatment failure, compromising future treatment options and leading to increased risk of mortality (World Health Organization, 2006). The World Health Organization (WHO) recommends regimens involving tablets and that syrup or liquid formulation be prescribed for children depending on weight, however recognizing that lack of refrigeration and the supply chain for syrup or liquid forms may bring some challenges (World Health Organization, 2010). Children and adolescents with HIV often face other life stressors that affect their ability to achieve optimum adherence, including parental HIV disease, poverty, and limited or inconsistent social support (Steele et al., 2007). Availability of adherence information assists health care workers in providing optimal care to patients.

In Tanzania, studies on adherence have been primarily focused on adults and less information is available on children and teenagers. As children form a special group due to lengthy expected time on ART and challenges faced during adolescence, more information is needed in order to design appropriate interventions to improve or maintain sufficient ART adherence levels. This study estimated adherence levels, investigated determinants for ART adherence and explored barriers and facilitators of adherence among children and teenagers in rural Tanzania.

METHODS

Study design

We used a sequential explanatory mixed methods study design. A quantitative cross sectional study was followed by a qualitative study combining focus group discussions (FGDs) and in-depth interviews (IDIs).

Study setting

We conducted the study in Ifakara town in the Kilombero district of the Morogoro region for 6 months between November 2011 and April 2012. The study was performed within the observational HIV cohort, Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), at the Chronic Diseases Clinic Ifakara (CDCI) in St Francis Referral Hospital (SFRH). The CDCI started providing HIV care and treatment in 2005 in Ifakara (Mossdorf, Stoeckle et al., 2011; Mossdorf, Stoeckle et al., 2010; Stoeckle, McHomvu et al., 2006) in accordance with guidelines of the Tanzanian National AIDS Control Program (NACP) (National Aids Control programme, 2005). Follow up visits are scheduled every 3-6 months. All patients were treated as per Tanzania National Guideline for HIV/AIDS treatment (NACP, 2008b). During the study, liquid formulations were only available for prophylaxis among HIV-exposed infants and not as treatment for HIV infected children. Early infant diagnosis (EID) was unavailable at CDCI during the study period but has been recently introduced.

Quantitative component

Study participants

We targeted all patients attending the CDCI who were on ART and aged between 2-19 years. Patients were included if they had visited the CDCI for a drug refill between 10-150 days prior to the start of the study. The study participants were traced and interviewed at home during an unannounced visit. For the quantitative data collection, children below 18 years were interviewed together with their parents/caretakers. We did not interview children who were critically ill.

Data collection

The interviews were conducted in Swahili, the national language of Tanzania and commonly spoken by Ifakara residents. For the quantitative study, data were collected by trained non-medical field interviewers using a structured questionnaire.

Variables

Outcome

The primary outcome variable was ART adherence. Percentage adherence was measured as the ratio of drugs actually taken to the drugs supposed to be taken (prescribed) by using the formula $[\text{Adherence} = (\text{Number of pills dispensed} - \text{Number of pills remained}) \times 100 / (\text{Number of pills prescribed per day} \times \text{number of days between pharmacy visit and home visit})]$. The drugs actually taken were estimated by calculating the number of dispensed drugs minus the drugs found during the unannounced visit. This was assessed using pill count, which was first calculated by field worker and then verified by a field manager. The overall average adherence was calculated in two steps. Since commonly used ART regimens involve a combination of three drugs and are dispensed as either a fixed dose or a separate combination, the adherence percentage level for each drug was calculated. Then the average adherence for each regimen was assessed for each individual. Participants were encouraged to provide all ART pills that were dispensed at the clinic in the last visit plus the ones that

remained from the prior visit. For individuals whose adherence levels exceeded 100%, the adherence level was capped at 100%. For the analysis, optimal adherence was defined as having taken $\geq 80\%$ of the required pills.

Predictors of ART adherence

The determinants for ART adherence were : gender, pill burden, visit to a local healer (who claimed to have a cure for HIV/AIDS), disease progression measured by age-specific immunological criteria (immune-suppressed if $CD4 < 500$ cells/ mm^3 for children aged < 6 years and if $CD4 < 350$ cells/ mm^3 for children ≥ 6 years) and WHO clinical staging (I/II versus III/IV), child awareness of HIV disease, parental status (both parents, single parent, or non-parental caretaker (non-parental caretaker included patients grandmother, sister, aunt, uncle or step mother)), distance to the clinic, duration under ART, knowledge about ART treatment duration, HIV support group membership, adherence assistance (parents versus others), socioeconomic status (SES) and education level. Education level was assessed by combining age and school attendance (preschool age (2-5 years), children of school age (6 years or more) who never went to school, children of school age and in school, children of secondary school age (12 years or more) but in primary school, and children of secondary school age and in secondary school).

Collection of socioeconomic status (SES) data

Data on socioeconomic status was collected using an asset survey from June 2011 to September 2011 among 1935 patients under ART enrolled in KIULARCO. ‘Low’, ‘middle’ and ‘high’ tertiles of socio-economic status were constructed using principal component analysis (Nikoi et al., 2013) on scores calculated from asset ownership (electricity, lamp, radio, television, mobile phone, land line, iron, refrigerator, wrist watch, bicycle, motor bike, motorcar, and having a bank account) and the house’ building materials (mud, bamboo, wood, tiles, cement, carpet, grass, post, brick (sun), brick (fire), wood, cement bricks, iron sheets, tiles, concrete and fabricated bricks).

Bias

Classification bias of adherence level was minimized by training field interviewers on how to assess and calculate adherence percentages as well as cross-checking adherence estimates for confirmation by a field manager before data entry. To reduce social desirability bias, information on level and determinants of adherence was collected by non-medical staff.

Sample size

We included all active patients aged 2-19 years under ART attending the CDCI within the last 150 days, i.e. 163 patients. Using an alpha of 5%, a power of 90% and a hypothesized adherence prevalence of 70% in the reference category, with this effective sample size we were able to statistically significantly detect a risk ratio of 1.4.

Data processing and analysis

Quantitative data were double entered using EPI-DATA (EpiData Association, Odense, Denmark) and analyzed using STATA 11.0 (STATA Corp., College Station, Texas, USA). Chi square test was used to assess the association between the variables studied and the response status and with the adherence categories. Logistic regression was used to estimate associations between adherence and risk factors. Participants with missing adherence (outcome) data were excluded from analysis. Sensitivity analyses were done to assess the potential influence of missing values for predictor variables. Variables with a P-value of less than 0.25 were eligible for inclusion in the multivariable analysis. Since this applied to only one variable (parental status), we reported only the univariate analysis. We assessed if non-response was associated with variables under the study. Variable(s) that were found to predict adherence were investigated in the qualitative part to understand the mechanism underlying such association.

Qualitative component

Population and Sample

We targeted adolescents aged 13-17 years who were on ART who were aware of their HIV status and the parent or non-parent caretakers in charge of the child. The Tanzanian definition of adolescents has been adopted from the WHO (World Health Organization, 2014) which defines adolescent as a young person aged between 10-19 years. However, for the purpose of this study, we interviewed adolescents of age 13 to 17 years assuming that these adolescents will be capable of expressing their views on issues related to treatment experience and challenges. From the CDCI database we randomly sampled boys and girls aged 13-15 and 16-17 and within each group conducted one FGD. In total we included 35 HIV infected adolescents in the FGDs. We also conducted FGDs with 21 parents or caretakers living with HIV infected adolescents (on ART) residing within the study site, two FGDs with women and two with men. Each FGD comprised of 7-8 participants. We opted for the FGDs due to their usefulness in enhancing social interaction different from other qualitative methods (Merton et al., 1990), high face validity (Krueger, 1988) and their relevance in providing opportunity to interview several participants systematically and simultaneously (Babbie, 2011). To deepen our understanding of issues emanating from FGDs, we subsequently conducted four IDIs, with a 16 year old male patient, a 43 year old male caretaker of an eight year old child and with two healthcare providers (a medical doctor and a nurse).

Data collection

An interview topic guide with specific themes aided the FGDs. The was guide composed of broader themes that relate to attitude and perception on ART, perceived benefit of ART treatment, perceived risk of treatment, knowledge about treatment adherence, family strategies to ensure treatment adherence, children's experience with treatment and perceived barriers to treatment adherence. Interview topics were drawn from the relevant literature (Li et al., 2010), health behavior theories (Ajzen et al., 1980; Rosenstock, 1966) and life

experience/observation. The second author who is a female social scientist facilitated the discussions aided by a trained male research assistant. To enhance freedom of expression during FGDs, participants' were facilitated by researchers of matching sex and in a neutral venue, i.e. at a school after school hours. The discussions were audio recorded following permission from the participants. Throughout the interview, free flowing discussion was encouraged and some new topics which were raised in the first interview were again probed in the next interviews following the principles of grounded theory (Ajzen & Fishbein, 1980). Unlike adults, children's explanations about barriers to treatment adherence were in short segments, sometimes not very direct but useful. The researcher took time to probe and motivate children to provide their inside views and experience that relates to taking the lifelong treatment.

Data Analysis

After the interviews, the research assistants transcribed verbatim digitally audio recorded interviews in Swahili language. The second author frequently reviewed the transcripts using the side notes and relevant ideas were noted. Thematic content analysis was used to process all participants' descriptions along with identification of relevant concepts and ideas found in the transcripts linked to the topics of inquiry (Anderson, 1997).

Relevant ideas were categorized under specific themes and later coded (LeCompte et al., 1994). We included the pre-existing themes, for example "attitude towards ART treatment" and "non-parental care". We also included emerged themes such as "supportive school environment" and "unfriendly nature of counseling services".

Ethical statement

The study received ethical clearance from National Institute of Medical Research of Tanzania. Parents and caretakers signed the informed consent to participate in the study, both for themselves and on their children's behalf. Participating children assented to answer questions. Records were anonymized and patients were identified by unique identifiers during

analysis and reporting. As per routine procedures in the clinic, patients who had poor adherence levels were further followed up by physicians in the CDCI.

RESULTS

Data flow

There were 265 HIV patients <20 years of age attending the clinic of whom 163 (62%) were currently on ART (Figure 1). Forty patients (25%) were not interviewed because of refusal, non-availability or death. The reasons for non-availability were undocumented transfer, an incorrect home address or travel of the patient. For the quantitative study, we interviewed 123 (75%) of 163 patients approached. Among the patients successfully interviewed, seven were excluded from the analysis because they did not have adherence data (they did not provide their pills during the home visit). We finally included 116 children and adolescents in the analysis (Figure 1). Non-response was not associated with the variables under study (Table 3).

Study participants characteristics

Sixty-seven (58%) of the participants were males. The median age was 9.8 years (interquartile range (IQR): 5.7 – 13.3, range 2 - 19), and 77 (66%) of the participants were not living with both parents (out of these, 61% (47/77) were not living with either parent). Patients had been taking ART for a median of 35.8 months (IQR: 23-46) (Table 3). All participants were taking first line treatment regimens based on 2 NRTIs+1 NNRTI.

Adherence levels

The overall average ART adherence level was 84.2% with a range from 2.3% to 100% and the proportion of patients with adherence level of 80% or more was 70% (81/116).

Determinants for adherence

From the logistic regression analysis, children living with non-parent caretakers were more likely to have poor adherence compared to children living with their parents ((OR=2.84, 95% CI: (1.04-7.77)) (Table 4). Children living with single parent or non-parent caretaker had lower levels of optimal adherence compared to children living with biological parents. The

magnitude of association between adherence and educational status was high, but the evidence of association was statistically non-significant (children of primary school age (6 years or more) who never went to school compared to preschool age children, OR=2.39, 95% CI: (0.69-8.28)). Children who reportedly joined an HIV support group had a lower proportion of optimal adherers compared to children who were never members (OR =2.0, 95% CI 0.75-5.27). The quantitative analysis showed no associations between adherence levels and sex, education, duration on ART, CD4+ T cells count, WHO clinical staging, SES, ever visited traditional healer, pill burden and disclosure status.

Barriers and facilitators of adherence

The results of the FGDs and IDs complemented the cross-sectional survey and shed further light on its findings. The thematic analysis suggested a range of themes influencing adherence to ART, many of which were commonly shared among the FGD and IDs participants.

Facilitators of treatment adherence

Positive attitudes and perceived benefits towards treatment

Both children and caretakers reflected a positive attitude towards treatment. This was indicated by the adolescent's expression of "*feeling good with the treatment*" which was a common statement by most of the children. Caretakers shared the same experience "*we become happy when we see health improvement of our children*".

Positive attitude towards treatment was also reflected by the experiences reported by the groups in relation to the perceived benefits of treatment. The most recurrent themes related to the perceived benefits of treatment included the '*reduction of recurrent diseases*', "*looking healthy after the initiating ARV*", "*living longer*", "*getting cured*", "*ability to participate in economic activities*" and "*ability to attend classes*".

The following excerpts indicate some of the related themes:

"My son used to be sick every day, and he was very thin, but after treatment initiation I can see that he is now well, but I can see other children also, before they start

treatment they become very sick but after treatment they change (their health status).
[FGD, Female].

“Ooh, the treatment is good, like me I wasn’t like this, before taking this treatment I had rashes all over my body and I was so thin until my fellow children were avoiding me and said she has AIDS, but when I started taking the medicine, my condition changed and I am now big and healthy”. [FGD, Girl].

Knowledge about treatment adherence

Generally, participants were able to explain the meaning of treatment adherence conditions. The most frequently mentioned treatment adherence conditions included *“taking drugs in the morning and evening”*, *“taking drugs without stopping”*, *“taking drugs before food”*, *“eating fruits”* and *“abiding to the time of taking drugs without changing”*.

For those who were able to mention the risks of non-adherence to treatment, they mostly mentioned recurrence of illness, suffering and death as reflected in the following excerpts:

“Following treatment instructions it means taking drugs every day because at times the body is used to that. When you stop abruptly the body will get problems because it will notice the difference. And the body will get fevers which were over”. [FGD, Female].

Treatment adherence barriers

Despite respondents clearly valuing ART, several barriers existed for maintaining ART adherence in the social environment, in the health service delivery, and related to the treatment and disease itself.

Fear of stigma and consequences

Most caretakers and children were strongly opposed to sharing the child’s treatment status with other people, friends or relatives in the community due to fear of mocking by other people in the community. Most children and adolescents viewed taking their treatment pills in

front of their fellow children as unacceptable due to negative reaction from other children in the community:

“I can’t dare to tell any of my friends or neighbors that my child is on treatment, because they will start spreading this information to others”. [FGD, Male].

“When I take these drugs they (other children) will say, “We do not know what he is suffering from. He is taking drugs every day; but he is not getting cured”. [FGD, Boy].

Enacted stigma also contributed to a lack of a supportive school environment. The school mates and teachers mocked, segregated and stigmatized children with HIV taking ART. Some children reported that they initially used to take their drugs at school but have decided to change and begin to take drugs at home due to some insults from their fellow students.

“Parents fear disclosing their children’s HIV and treatment status to teachers because of fear that their children may be segregated. My child was pinned a red label on his shirt by his teacher after he knew the HIV and treatment status of the child”. [FGD, Male].

“In the past fellow schoolmates started mocking at me that I have AIDS after they saw me taking ARV at school. Later I had to change and started taking the pills at home”. [FGD, Girl].

Non-parent caretaker

According to the FGD discussants, children who live with their biological parents receive much more treatment support and care as compared with children who live with their caretakers.

“Step mothers contribute also to poor adherence. At times it happens that you are sick and the father asks the mother to take you to the hospital. When dad goes to work, the step mother doesn’t take me for treatment and I continue suffering”. [FGD, Boy].

Health service delivery factors

Some children and caretakers expressed their concern about the counseling sessions offered at the health facility which combined adults and children all together. Children felt that they need to have separate counseling sessions so they can express their treatment challenges freely without having adults interfering and can receive the attention they need from the counselors.

“They combine us (children) with those (adults), when we are there with them (adults) we cannot understand things (information) and some of us cannot ask questions or explain problems.... There should be some separate sessions for children and so the doctors could listen nicely to children”. [FGD, Boy].

Not informed about HIV status

Some children expressed their concern that they were not informed about their HIV status by their parents. One child described his concern as follows:

“I grew up taking medicine without knowing the disease that I was suffering. They kept on telling me that I have malaria and until now they have not told me anything with regards to HIV, but the doctor told me that I am HIV positive and I feel bad that my sister did not tell me”. [FGD, Boy].

Some parents also explained difficulties faced in disclosing HIV status to their children but once informed the children were able to adhere with their treatment schedule, as explained by one parent in the following excerpt:

“I asked my child to take medicine without telling him what he was suffering from. When I told him what he was suffering from (HIV), it helped him to follow the instructions. I told him that his mother died because of the same problem and that he should not stop taking drugs”. [FGD, Male].

Preference of Traditional medicine

Some parents encourage their children to go beyond the formal health sector and take traditional medicine instead of drugs obtained at the health facility.

“Some parents do not want their children to take medicines from the hospital. They give them traditional medicines when it is obvious that the child has AIDS”. [FGD, Boy].

Inconvenient treatment schedule and longevity of the treatment (treatment fatigue)

Taking drugs in the morning before going to school was not very patient-friendly as children often forget while hurrying for school or felt sick if they were forced to take drugs before breakfast. One boy expressed the concern as follows:

“My mother tells me to take drugs in the morning and I sometimes wake up very early and no food prepared, and when I take medicine (in the morning) I feel nausea but I go to school just like that... and I try not to miss school...”. [FGD, Boy].

Children and caretakers gave the impression that some children are getting tired of taking the medications as explained below:

“Some grown-up children may sometimes cheat that they have taken drugs while they have not, because they are tired and the parents believe that they have already taken the drugs”. [FGD, Female].

“Some children are tired of taking medicine, I remember one day when I was giving my child medicine, and he told me that, ‘uncle if you want to give me medicine give me even those for tomorrow’”. [FGD, Male].

Forgetfulness and feeling better

Patients FGD discussants from both groups mentioned the problem of forgetting to take drugs at the appropriate time due to the intensity of their engagement in games. At times, especially when patients observe some health improvement, they do not have the motivation to continue with treatment.

“There are others (children) who put priority on games and when they are playing they forget to take drugs completely”. [FGD, Boy].

“You find another person goes to the hospital and when they are given drugs they take them for one month and in the next month they stop taking these drugs when they see that they are OK”. [FGD, Girl].

DISCUSSION

This explanatory mixed-methods study among children and teenagers attending a large HIV care and treatment clinic showed that participants had a positive attitude towards ART and 70% of the participants achieved desired level of adherence (defined as 80% or higher). The proportion of patients with acceptable levels of adherence varies across several studies using different techniques of evaluating adherence.

A review of ART adherence in low and middle-income countries found a range in adherence level estimates from 49% to 100% with 76% of articles reporting >75% adherence (Vreeman et al., 2008b). A study done in India showed 95.3% (Seth et al., 2013) of the children had acceptable level of adherence whilst a study done in Dar es Salaam showed 97% (Mghamba et al., 2013) of children had optimal adherence. Another study done in Ethiopia showed that 34.8% of the children had acceptable level of adherence when unannounced home visit was made (Biressaw et al., 2013). The wide difference here appears to be driven by the nature of the visits (announced versus unannounced or prior known visit). Possible explanations for a low adherence in our study might be: (a) by interviewing participants at home, we might have captured children who were at risk of being “lost to follow-up”; in clinic-based studies these children would not have been included; (b) we used non-medical staff to collect information which may have reduced social desirability bias; (c) measuring adherence by pill count usually shows low adherence levels compared to other methods such as self-report (Martin et al., 2009) and lastly (d) our study participants had an average treatment duration of 3 years, and as the qualitative part outline treatment fatigue was present.

Patients not staying with biological parents were more likely to have poor adherence. Other studies found that children’s adherence is affected by their dependence on caretakers and that

if adult caregivers are unavailable, the risk of missed doses increases (Marcus, 2006; Nabukeera-Barungi et al., 2007). The successful treatment of a child requires the commitment and involvement of a responsible caregiver yet qualitative findings showed that most often both parents and children are concerned with the stigma related to disclosure of HIV status to other family members or caretakers, friends and schools teachers thus restricting the child's options for seeking support (World Health Organization, 2010). According to our participants, the care given to HIV infected children by biological parents was not the same as that given by non-parental caretakers. This may be partly because some non-parental caretakers were unaware of the child's HIV status. In other studies, disclosure was related to improved adherence to ART medications and influenced children's participation in healthcare decision-making (Bachanas et al., 2001; Bikaako-Kajura et al., 2006; Blasini et al., 2004; Lesch et al., 2007). Health illiteracy might be another issue surrounding poor adherence levels. Compared to adults, children have lower levels of health literacy and thus, following health care providers' directives on maintaining adherence might not be easy for them (Marcus, 2006). In times when children focus too much on playing with friends, they tend to forget taking the drugs and the situation worsens if their caretakers are not present. Children who live with HIV-positive parents have the potential additional benefit of the parental experience in living with HIV and taking ART. However, we did not have information on the HIV status of parents or caretakers. Children with non-parental caretakers were older (median age 11.4 versus 8.3 years) suggesting that some adherence problems might be partially attributed to puberty. However these possible explanations should be investigated further.

Secondary school aged children who had only primary education or were still in primary school were more likely to be non-adherent, although the association was not significant. This may be partly explained by the fact that 50% of these children were living with non-parental caretakers, thus were at risk of less support to maintain adequate adherence levels. The study's qualitative part provides another explanation for these findings. The morning dose

was challenging for children attending school as they often have to leave for school early in the morning before breakfast is ready. Competing demand between taking the morning ART dose and rushing to school make them vulnerable to skip their medications. A study on how food insecurity impacts on non-adherence to ART found that side effects were exacerbated when taking ART in the absence of food (S. D. Weiser et al., 2010). However, our study's participants reside in a location where food supply is quite stable and food shortage was not reported as a barrier for optimal adherence in the qualitative component. It was rather the school environment where HIV patients experienced mocking and segregation which made it hard for them to take their ART while at school and led to missing the morning dose. In some settings HIV positive children attending school were given names by their colleagues so as to victimize them. In Namibia for instance, it was found that derogatory terms have been used to discriminate HIV students (Chinsembu et al., 2011). This impacts adherence levels as low social support (Halkitis et al., 2005) and stigma has been identified in previous studies to affect access to health care, social interaction and medication adherence (Carr et al., 2004).

The association between adherence and SES, although not significant, is in an unexpected direction; patients coming from affluent families are at higher risk of poor adherence. The effect of SES on adherence among HIV infected patients is considered a controversial issue (Fong et al., 2003; Goldman et al., 2002; Ickovics et al., 2002). Suggested pathways in which socioeconomic status might be associated with adherence include education's effect on shaping a financially stable future, and on acquiring health literacy and knowledge to use health resources, while income plays a big part in obtaining better housing conditions, recreational facilities and better health care (Adler et al., 2002). However, a systematic review of the evidence regarding the association of SES with adherence to treatment of patients with HIV/AIDS found no conclusive support for existence of a clear association between the two variables (Falagas et al., 2008). From the explanatory qualitative study, barriers of optimal adherence were unfavorable school environment, patients being unaware of their own HIV

status, children feeling too shy to go to collect medication at the clinic, parents' failure to disclose the children's HIV status to family members/caretakers and differential care from non-parental caretakers.

Strengths and limitations of the study

Apart from the strengths aforementioned, using a mixed methods design allowed explanation and in-depth understanding of the quantitative results. The patients were set in programmatic conditions i.e. not in a clinical trial cohort with intensive support. The study covered a wide time window, thus increasing generalizability and reducing potential seasonality bias.

In addition to limitations of the methods used for measuring adherence, selection bias may have resulted from the rather high non-response rate of 25%. However non-response analysis showed that variables under study were not associated with non-response. In addition, we performed sensitivity analysis (data not shown) for predictor variables with missing information and the results were not considerably affected except WHO staging. However WHO staging was taken from the clinic database (and not the home visit) and was often missing due to drug refill visits by someone other than the patient. In some studies, pill count has been found to predict response to ART (Liu, Golin et al., 2001), particularly when conducted with no prior notification. However, in other studies, it has been shown to be liable to pill dumping (Feinstein, 1990), fabrication, and manipulation. Grouping a cohort of 2-19 year olds together might have disguised specific adherence challenges for younger children (palatability, caregiver availability), which are very different from the challenges for teenagers.

Implications

The implications of poor adherence for these children might be that they experience worse clinical outcomes. If this situation extends beyond our immediate setting, both the current and future treatment options are under threat if appropriate actions are not put in place to address adherence issues in children and teenagers. A systematic review showed that almost a

quarter of patients fail second-line therapy within 12 months, mainly because of poor adherence rather than drug resistance (Ajose et al., 2012). As this age group (12+yrs) is becoming sexually active, the likelihood of transmission of HIV increases when the drugs are not taken properly and the virus is not suppressed (Cohen et al., 2011). New efforts have to be made and fully implemented to boost adherence to ART in this important population.

The following recommendations could help improve adherence among children and teenagers in settings similar to ours: Parents and/or caretakers should counsel and guide children on taking drugs parallel with providing a supportive environment at home i.e. family supporter to ensure that during the parent's absent children are able to maintain good adherence. Caretakers should create conducive environment at home for children i.e. make sure that food is ready before the child take his/her dose especially in the morning. Counsellors should improve counselling techniques and focus more on how to overcome challenges that make children not take their drugs as required. Furthermore, children should have age-specific counseling services at HIV clinics separate from adults. This can be done at the HIV clinic or at home during home-based care (HBC) visit. Assigned caretakers (parents or non-parents) should disclose their children's HIV and ART status to household members who will be able to provide support to children when parents are absent. Health promotion messages should be tailored to specific groups such as teachers, fellow students as well as general community members to reduce their stigmatizing behavior towards HIV positive children. Advocacy for the formulation of peer support groups in the community and in schools should be encouraged to take a lead in advocating for love, care and support for HIV infected children.

Conclusion

In conclusion, evidence from this study suggests that, children not living with both parents, are more likely to have worse adherence to ART, in part due to an inadequate support environment in school and within the nuclear or extended family.

Competing Interests: There is no competing interest to declare.

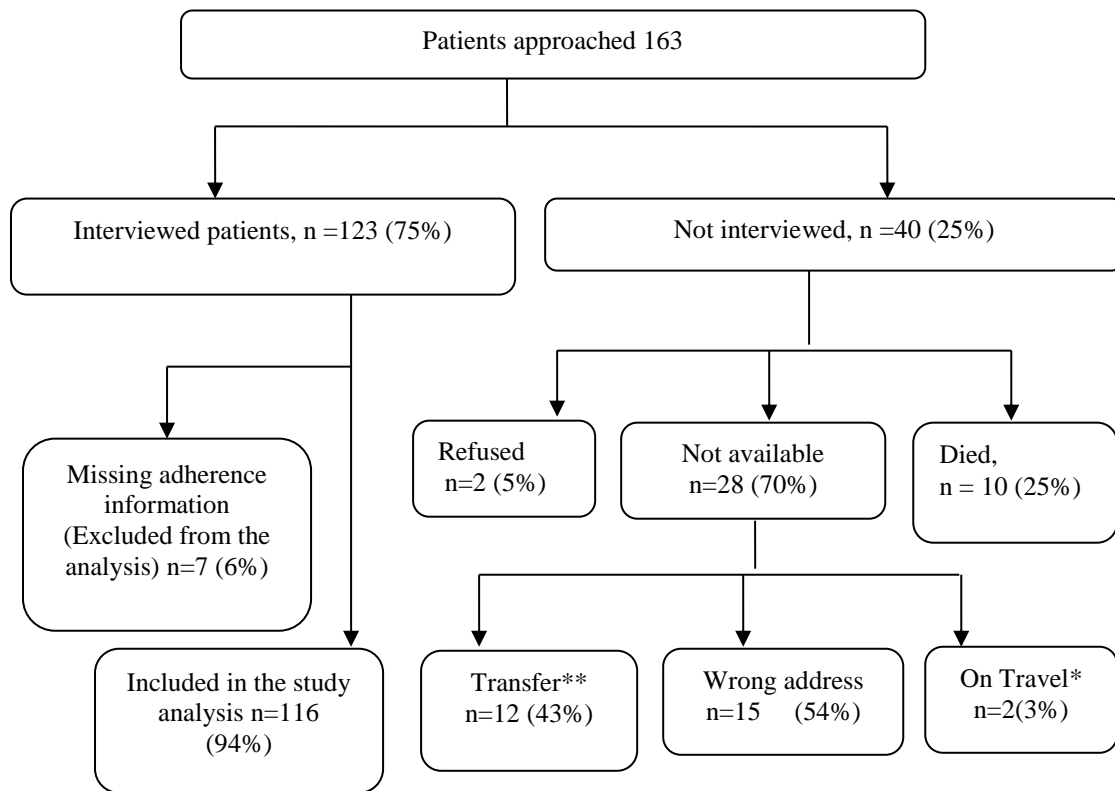
Author contribution:

DN conceptualized, designed and conducted the study, supervised data collection, analysed and wrote the manuscript. SM conducted the qualitative component of the study and was involved in preparing the manuscript. LH, FF, TG, EL, MT were involved in the design, analysis and preparation of the manuscript. EG conceptualized and designed the study and helped with the analysis and manuscript writing. All authors approved the final version of the manuscript.

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Figure 2: Flow diagram of the study participants



* On Travel meant the patients was not within Ifakara town. Subjects had traveled outside Ifakara for various reasons

**These are patients who transferred out without having transfer permit from the clinic

Table 3: Summary of characteristics of patients by response status

Variable	Responders		Non-Responders		P-Value
	n	%	n	%	
Sex					
Male	67	58	24	51	0.40
Female	49	42	23	49	
Age categories (yrs)					
2-5	30	26	16	34	0.51
6-11	46	40	15	32	
12+	40	34	16	34	
WHO stage					
Stage I & II	31	27	14	30	0.59
Stage III & IV	40	34	27	57	
Missing	45	39	6	13	
Distance to clinic					
<5km	93	80	43	91	0.08
>5km	23	20	4	9	
Duration on ART (yrs)					
0-2	46	40	11	23	0.43
>3	60	52	20	43	
Missing	10	9	16	34	
WHO stage= World Health Organization clinical stage; yrs=years; km=Kilometres; %= Column percentages					

Table 4: Summary of characteristics of participants by adherence categories

Variables	Optimal		Suboptimal		P-Value
	n	%	n	%	
Sex					
Male	46	69	21	31	0.75
Female	35	71	14	29	
Age-school					
Pre-school age 2-5yrs	23	77	7	23	0.74
>6yrs never been to school	11	58	8	42	
Primary school age and in primary	21	70	9	30	
Secondary school but in primary	19	70	8	30	
Secondary school age and in secondary	7	70	3	30	
Baseline CD4 + cell count					
Below 350 cells/mm ³	33	66	17	34	0.54
Above 350cells/mm ³	42	71	17	29	
Missing	6	86	1	14	
Age specific immunosuppression					
Not Immunosuppressed	61	70	26	30	0.83
Immunosuppressed	16	67	8	33	
Missing	4	80	1	20	
Duration under ART					
0-2 yrs	30	65	16	35	0.09
>2 yrs	41	68	19	32	
Missing	10	100	0	0	
Parental status					
Both parent	32	82	7	18	0.11
Single parent	20	67	10	33	
Non-parental caretaker	29	62	18	38	
Knows that treatment is lifelong					
Yes	57	70	24	30	0.85
No	24	69	11	31	
Disclosure of HIV status					
Yes	25	64	14	36	0.29
No	53	75	18	25	
Missing	3	50	3	50	
Adherence assistance					
Parents	48	74	17	26	0.29
Non-parental adherence assistants	33	65	18	35	
Visited traditional healer for HIV cure*					
Yes	15	75	5	25	0.28
No	66	69	29	31	
Missing	0	0	1	100	
Pill Burden					
1 pill	35	69	16	31	0.80
2-3 pills	46	71	19	29	
Joined any HIV support group					
Yes	12	57	9	43	0.16
No	69	73	26	27	
WHO clinical staging					

Stage I & II	20	65	11	35	
Stage III & IV	26	65	14	35	
Missing	35	78	10	22	0.33
Socioeconomic status					
Low	30	73	11	27	
Median	16	73	6	27	
High	27	63	16	37	
Missing	8	80	2	20	0.61
<p>Poor adherence=less than 80%;optimal adherence=80% or more; WHO= World Health Organization;yrs=years; * visited a healer who claimed to have a cure for HIV/AIDS; Immune-suppressed if CD4 <500 cells/mm³ for children aged <6 years and if CD4<350 cells/mm³ for children aged 6 years and above;%=Row percentages; p=Chi2 P-value</p>					

Table 5 Univariate logistic regression of predictors of poor adherence among children

Univariate analysis			
Variable	OR	95% CI	P-Value
Sex			
Female	0.88	0.39-1.96	0.748
Age-School			
Pre-school age 2-5yrs	1		
>6yrs never been to school	2.39	0.69-8.28	0.170
Primary school age and in primary	1.41	0.45-4.45	0.560
Secondary school age but in primary	1.38	0.42-4.5	0.591
Secondary school age and in secondary	1.41	0.29-6.9	0.674
Baseline CD4 + cell count			
Below 350/mm3	1		
Above 350/mm3	0.79	0.35-1.77	0.561
Age specific immunosuppression			
Not Immunosuppressed	1		
Immunosuppressed	1.17	0.46-3.08	0.746
Duration under ART			
0-2 years	1		
>2 years	0.88	0.38-1.96	0.735
WHO stage			
Stage I & II	1		
Stage III & IV	0.98	0.37-2.61	0.966
Visited Traditional Healer for HIV cure*			
No	1		
Yes	0.76	0.25-2.28	0.623
Pill burden			
1 pill	1		
2-3 pills	0.90	0.41-2.0	0.803
Disclosure of HIV status			
Yes	1		
No	0.61	0.26-1.41	0.246
Joined any HIV support group			
Yes	2.0	0.75-5.27	0.166
Adherence Assistance			
Parents	1		
Non-parental adherence assistants	1.54	0.69-3.41	0.288
Knows that treatment is lifelong			
No	1		
Yes	1.65	0.71-3.84	0.246
Socio-economic status			
Low	1		
Median	1.02	0.32-3.3	0.970
High	1.62	0.64-4.08	0.310
Parental status			
Both Parents	1		
Single parent	2.29	0.75-6.98	0.200
Non-parental caretaker	2.84	1.04-7.77	0.042

*Visited a healer who claimed to have a cure for HIV/AIDS; Poor adherence=less than 80%;optimal adherence=80% or more; Immune-suppressed if CD4 <500 for children aged <6 years and if CD4<350 for children aged 6 years and above; WHO=World Health Organization; yrs=years; CI =confidence interval; OR=odds ratio.

CHAPTER FIVE: Adherence among patients attending a rural HIV clinic in Tanzania

ABSTRACT

Introduction

Adherence to antiretroviral therapy (ART) is one of the most important and one of the only modifiable risk factors that affect treatment success. Our objectives were to describe ART adherence and to find determinants of non-adherence among patients enrolled in the Kilombero-Ulangu Antiretroviral Cohort in rural Tanzania.

Methods

A longitudinal study design including all patients on ART attending the clinic between June 2011 and May 2012 was used. We collected information about adherence during the previous month. Non-adherence was defined as missing any ART dose in the month prior to the interview. To identify determinants of non-adherence over time, we constructed repeated measures logistic regression models.

Results

We interviewed 2146 patients during 9295 clinical visits over 12 months of follow-up. Overall the non-adherence level was ranging between 3.5 to 9.9%. Determinants of non-adherence were the shorter duration on ART, having a low socio-economic status and living closer to the clinic.

Conclusion

Adherence levels reported over time appear satisfactory in this rural, rather dispersed HIV-treatment cohort during the study period. Additional efforts to improve adherence should target patients in the first weeks or months of ART initiation and with a particular focus on patients with low socio-economic status.

BACKGROUND

There were 35.3 million people living with human immunodeficiency virus (HIV) in 2012 (WHO, 2013b). Furthermore, 2.3 million new infections and 1.6 million deaths due to HIV occurred in 2012 (UNAIDS, 2013b). Sub-Saharan Africa is one of the regions most affected by morbidity and mortality from infection with HIV and has approximately two thirds of the world's HIV infected persons (UNAIDS/WHO, 2008). In Tanzania, the estimated adult HIV prevalence was 5.1% by 2012, after a decrease from 5.7 in 2004 (TACAIDS, 2009b). Starting with the introduction of potent antiretroviral therapy (ART) in 1996, HIV changed from being a death sentence to a more manageable chronic illness. Increased political commitment and smarter investments, together with more strategic programming and massive reductions in the cost of treatment have led to a record 9.7 million people in low- and middle-income countries having access to antiretroviral therapy by the end of 2012 (UNAIDS, 2013b). The Tanzania HIV Care and Treatment Plan was launched in October 2004, aiming at providing 440,000 AIDS patients with ART and tracking disease progression in 1.2 million HIV positive subjects by the end of 2009 (G. Somi et al., 2009). According to the World Health Organization (WHO) report on HIV treatment in 2013, only 40% of Tanzanian children and adults in need were receiving ART (WHO, 2013a). The main constraints for access to ART in Africa have been lack of infrastructure to procure and distribute drugs, inadequate numbers of trained health care staff, and the lack of adequate laboratory facilities to monitor patients receiving ART (Nkengason J. N, 2004).

According to recent studies, ART regimens require 70–90% adherence in order to be effective (Nachega, Mills et al., 2010). The goal of modern ART is long-term HIV RNA suppression, enabling immune reconstitution, reducing HIV drug resistance and preventing clinical disease progression (Bangsberg, Moss, et al., 2004; Bangsberg, Porco, et al., 2004; Hammer et al., 2006; Lima et al., 2009; Lima et al., 2008). Although ART is effective in reviving patients' health and improving quality of life, there are several challenges associated with the

treatment. Irregular and incomplete drug dosing is common despite the efforts of providers, pharmaceutical manufacturers, and health systems to encourage adherence. Non-adherence to antiretroviral therapy in adult populations has been shown to range from 33%–88%, depending on how adherence is defined and evaluated (Friedland G, 1999). Adherence has been found to be the most important modifiable factor that affects treatment outcome because failure to adhere to prescribed HIV therapy may result in treatment failure (Glass et al., 2008; Nieuwkerk et al., 2001; Paterson, Swindells et al., 2000), development of drug-resistant strains (Bangsberg, Charlebois et al., 2003; Harrigan, Hogg et al., 2005; Parienti, Massari et al., 2004; Sethi AK, Celentano DD et al., 2003; von Wyl et al., 2013), worsening of the disease (Honghu Liu, 2001), death (Wood E, 2003) and increasing health care costs (McDonnell PJ et al., 2002).

Because maintaining optimal adherence to sustain viral suppression over a lifetime remains a major challenge, there was a need to study adherence over time so as to design appropriate measures to improve ART uptake. We investigated factors that predict non-adherence among patients enrolled in an ART cohort in rural Tanzania.

METHODOLOGY

Settings

The study was conducted in Ifakara town in the Kilombero district of the Morogoro region in the observational open HIV cohort (KIULARCO), at the CDCI in St Francis Referral Hospital (SFRH) (Mossdorf, Stoeckle et al., 2011; Mossdorf, Stoeckle et al., 2010; Stoeckle, McHomvu et al., 2006).

Study design and plan

The study was longitudinal in design and targeted all registered patients on ART attending the CDCI between June 2011 and May 2012. Eligible patients were interviewed during routine clinical visits. During each visit, detailed information on ART adherence was collected in addition to the routine data collection. The study staff was trained in interview techniques to

minimize recall and social desirability bias. The study baseline was defined as the date of registration at the CDCI. Patients were followed until they were loss to follow-up (defined as those who joined the study but were not seen the last three months before the study ended) or the study ended.

Treatment initiation at CDCI

During the study period, all patients with CD4 count <350 cells/ μ l of whole blood, patients with WHO stage IV regardless of CD4 count, and pregnant women with WHO stage III or IV regardless of CD4 count were eligible to start ART (WHO, 2010b). Additionally, patients were required to come to the clinic with an adherence assistant who was to help the patients take their ART correctly. After treatment initiation, patients are required to visit the clinic on monthly basis for drug refill.

Outcome

The outcome of the study was adherence as measured by self-report. The adherence questionnaire was filled out during an interview by study staff. The adherence questionnaire recorded missed doses in the past three days and the past month prior to the interview, reasons for skipping medications, and if the patient ever changed or substituted the regimen (Appendix 1). A question regarding treatment interruption (if the patient ever stopped the drug in the previous 12 months) was added to the original questionnaire in December 2011. Non-adherence was defined as missing any ART dose in the past month prior to the interview. Optimal adherence was defined as not missing any ART dose in the month prior to the interview.

Predictor variables

The following variables recorded during ART initiation (at baseline) and during clinical visits (follow-up) were considered as predictors in our study:

The baseline variables were gender, marital status, age, travel distance to the clinic, socioeconomic status (SES), smoking, alcohol consumption (defined has said to drink

alcohol), functional status, WHO clinical staging. The follow-up variables were years attending CDCI, change in ART, type of non-nucleoside reverse transcriptase inhibitor (NNRTI), time on ART (measured by the number of visits), functional status, history of chronic illness (tuberculosis infection, hypertension, cancer and diabetes) , time on study (measured by frequency of interviews) and WHO clinical staging.

Collection of socioeconomic data

We collected data on socioeconomic status (SES) once using an asset survey from June 2011 to September 2011 among 1935 patients under ART in KIULARCO (Appendix 2). SES was assessed by constructing a household ‘wealth index’ based on scores calculated from asset ownership and building materials. This approach used principal component analysis (PCA), which transforms a number of correlated variables into a smaller number of uncorrelated variables (Filmer et al., 2001; Vyas et al., 2006). PCA allows variables that are collinear to be grouped together to form a composite index capable of representing the group of variables itself. Ownership of the following assets was considered: electricity, lamp, radio, television, mobile phone, land line, iron, refrigerator, wrist watch, bicycle, motor bike, motorcar, and having a bank account. Building materials considered were mud, bamboo, wood, tiles, cement, carpet, grass, post, sun-dried bricks, fired bricks, cement bricks, wood, iron sheets, tiles, concrete and fabricated bricks. The first component of the PCA was considered to represent SES and the score was divided into tertiles as low, middle, and high SES (Nikoi & Odimegwu, 2013).

Data processing and analysis

Data were double-entered and verified using EPI-DATA (EpiData Association, Odense, Denmark) and analysed using STATA 12.0 (STATA Corp., College Station, Texas, USA). Baseline characteristics were summarized using mean, median and percentages. To identify determinants of adherence over time, we constructed repeated measures logistic regression models. Generalized estimating equations were utilized to account for the clustering due to

the repeated responses in the same individuals. Results were presented with odds ratios (OR) and 95% confidence intervals (CI).

Ethical statement

The study was undertaken as part of the KIULARCO (Mossdorf Erik et al., 2011) operational research that received ethical and research clearance from the Ifakara Health Institute Institutional Review Board, the National Research Ethics Committee, Medical Research Coordination Committee of the National Institute for Medical Research (NIMR) through the Tanzania Commission for Science and Technology (COSTECH). Patients provide written consent upon entering the cohort. We also obtained oral consent from each participant interviewed in the study.

RESULTS

Data Flow

Of the 2146 participants on ART registered in KIULARCO and attending the CDCI during the study period, all agreed to participate in the study. Over the 12 month study period, we conducted 9295 interviews. Patients were interviewed during scheduled and unscheduled CDCI visits with a median number of 3 (IQR: 2-4) visits. A total of 556 (25.9%) were lost to follow-up before the study ended.

Baseline characteristics

The study was composed of 67% females, 43% aged between 20-40 years, 34% had high SES, 14% had an history of comorbidities, 46% were married or cohabiting, 59% were residing 5 km or less from the CDCI, 69% were in WHO clinical stage I and II, 28% reported to drink alcohol, 13% reported to smoke cigarette, 88% had nevirapine-based ART as their initial regimen and 17.8% had history of comorbidities as summarised in Table 6.

Non-adherence and treatment interruptions

Among the visits with a non-missing outcome observation, 3.5% (326/9281) reportedly missed an ART dose in the previous 3 days, 9.1% (837/9237) did not miss a dose in the

previous 3 days but missed a dose in the past month and 9.9% (922/9281) missed at least one dose in the month prior to the interview. At least 12.5% of participants reported to have missed a dose in the past 3 days and in the past month prior to the interview. Non-adherence reporting was less frequent in November 2011 and in the fourth visit. Non-adherence reporting was more frequent in September 2011 and in the eighth visit as shown in figure 1. The main reasons for missing doses were forgetfulness (48%), running out of pills (19%) and being away from home (17%) as shown in in table 2. During the study period, 8.8% (188/2146) of the participants reported to have interrupted ART during the previous year (Table 8). The median duration of ART interruptions was 15.5 days (IQR: 7-90).

Univariate and multivariate regression

In the univariate analysis, risk factors for non-adherence during the 12 month study were low SES, shorter duration on ART, younger age, time on study and poor clinical status (lower functional status). After adjusting for all prior selected variables of interest lower SES, shorter duration on ART, travel distance to the clinic and time in the study predicted non-adherence. For each additional year on ART at baseline (ART initiation), an individual was 11% less likely to report non-adherence (OR: 0.89, 95% CI: 0.81-0.96). Although not statistically significant, study participants with low SES were more likely to report non-adherence (OR: 1.29, 95% CI: 0.95-1.74) compared to patients with high SES. Patients residing more than 5 km from the clinic were less likely to report non-adherence levels (OR: 0.79, 95% CI: 0.61-1.03) compared to patients residing within 5 km from the clinic (Table 9). The relationship between number of interviews and adherence reporting was U-shaped showing optimal adherence reporting was highest at the initial interview(s) then declined during the subsequent visits before improving in the last visits of the study. Residing near the CDCI and smoking were the risk factors for treatment interruptions (Table 9).

DISCUSSION

This longitudinal study found that patients on ART for longer periods, time participating in the study and travel distance (to the CDCI) were associated with adherence to ART.

The study had a large sample size (>2000) and followed patients over a long period (up to 12 months) in a programmatic setting (no intervention, no additional visits). The study may have been subject to recall and social desirability bias but we trained staff in interview techniques to try to minimize these potential biases. The drugs used during the study were not recorded as fixed combinations but as separate drugs, which made assessing the effect of pill burden on adherence practically impossible. Patients reported good adherence during the 12 months of the study with only 12.5% of participants reported to have missed a dose during follow-up and 8.8% had experienced treatment interruptions. This is in line with studies done in Africa settings that report high adherence (Amberbir, Woldemichael et al., 2008; Bangsberg et al., 2001; Coetzee, Boulle et al., 2004; Oyugi, Byakika-Tusiime et al., 2004; S. Weiser et al., 2003). Despite challenges with access to ART, patients in developing countries and particularly also in peripheral health systems settings achieve remarkable adherence levels similar to or higher than those of patients in developed countries (Orrell et al., 2003). The adherence levels achieved reflect the success of the strategy to engage with individual adherence assistants as a prerequisite to initiate ART as established for this large ART-cohort since its inception in 2005 (Mossdorf, Stoeckle et al., 2011; Mossdorf, Stoeckle et al., 2010; Stoeckle, McHomvu et al., 2006). Non-adherence to ART followed the agricultural cycles and reflect how people set their individual priorities when basic needs need to be met. This interesting finding will be explored further to improve all Information Education and Communication (IEC) efforts as well as training of health staff and treatment assistants. The main reasons reported for missing doses of ART among our participants were forgetfulness and running out of pills, which is very similar to studies done in other rural and urban settings of Africa (Habib et al., 2010; Tiyou et al., 2010) and the United States (Amico et al., 2007)

but different from a study done in Europe (Italy) which found that confusion and poor psychological well-being were reasons for missed doses (Murri et al., 2000).

Our study has shown that more experienced patients reported better adherence compared to less experienced individuals. This is similar to studies done in Nepal (Wasti et al., 2012) and in the Therapeutics, Research, Education and AIDS Training in Asia (TREAT Asia) Studies to Evaluate Resistance Monitoring (TASER-M) (Jiamsakul, Kumarasamy, et al., 2014). A study done in the United Kingdom also revealed that adherence did improve over a median of 4.5 years (Cambiano et al., 2010). This might be due patient's delay to incorporate HIV infection and treatment status into self-identity. Initial reactions to HIV diagnosis include shock, fear, denial, or relief followed by post-diagnosis turning point which is often initiated by a person need to access ART (Baumgartner, 2007; Baumgartner et al., 2009). Some HIV patients believe HIV medication is necessary only when one is sick (Fagan et al., 2012) and this is evident because most HIV positive clients present to the clinic when the disease is at an advanced stage (Antinori et al., 2011). Since our study was longitudinal and attrition increases over time, a larger proportion of longer term ART users has dropped out of KIULARCO prior to start of this study than for short term users. Since the drop-outs are also more likely to have been non-adherers (because non-adherence increases risk for mortality and Lost to follow-up (LTFU), the group of long term ART users is a biased selection of the better adhering patients.

The study has shown that patients residing far from the clinic are less likely to report non-adherence. This is most interesting since it is generally expected that people from far should report lower adherence since the areas may not be well-resourced (Harvey et al., 2008). Studies have shown that in rural settings, optimal adherence tends to increase over time (Birbeck et al., 2009). Since rural populations live in a more communal setting, the positive impact of ART on HIV positive-patients might be more visible, which may positively influence optimal adherence. The association between distance and non-adherence might also

be explained by the fact that patients coming from outside Ifakara town incur more time and cost and hence have a sense of utilizing the opportunity to the fullest. They might be afraid that failure to adhere to drugs might increase their chances of developing other comorbidities which will add be more cost burden on to them. We are currently investigating these possibilities further.

Study participants with low SES were more likely to report lower adherence levels compared to those with high SES. This association might be linked by the fact that patients with low SES have inability to get enough and/or quality food as seen in previous studies (Berhe et al., 2013). Individuals on ART who lack resources are prone to malnutrition due to inadequate dietary intake, appetite loss, nutritional losses, metabolic changes, and increased requirements for both macro and micro-nutrients (Ivers et al., 2009). A study done previously in Botswana, Uganda and Tanzania found that a quarter of patients on ART fail optimal adherence due to nutritional, social and economic conditions (Hardon, Akurut et al., 2007). Patients with low SES are more likely to have excessive sedentary lifestyle, unhealthy dietary habits and excessive alcohol consumption. Because of the pronounced prevalence of unhealthy lifestyle among the poorest, they have often been blamed for having inappropriate health behaviors that may prevent them from seeking the care that they need (Jones et al., 1998). In other study settings, parameters of SES have been associated with non-adherence. Lower education is consistently associated with lower HIV medication adherence across geographic and economic settings (Fogarty et al., 2002; Rachlis et al., 2011).

In conclusion, we have systematically identified low SES, ART naïve and Proximity as predictors of non-adherence. Furthermore the study has shown good adherence reporting during agricultural periods. Additional efforts through targetted IEC should focus on (i) patients at the start of ART, i.e. in the first weeks, and (ii) the poor patient segments.

Table 6: Patients baseline characteristics

Variables	N (%)
Sex	
Female	1436 (67)
Males	695 (33)
Age (years)	
0-20	215 (10)
21-40	923 (43)
>40	994 (46)
Age (years)	
Mean (SD)	38.2(13.6)
Median (IQR)	39.1 (32-46.6)
Marital Status	
Married/Cohabiting	945 (46)
Single/Never married	609 (29)
Divorced/Separated/Widowed	515 (25)
Distance from home to CDCI	
<=5km	1021 (59)
>5km	878 (41)
WHO clinical stage	
Stage I & II	1468 (69)
Stage III & IV	649 (31)
Smoking	
Yes	264 (13)
No	1732 (87)
Alcohol consumption	
Yes	555 (28)
No	1442 (72)
Functional status	
Working	1904 (92)
Ambulatory/Bedridden	155(8)
Duration attending CDCI (months)	
Mean (SD)	5.5 (10.5)
Median (IQR)	0.87 (0.17-5.2)
Duration living with HIV (Months)	
Mean (SD)	7(13.4)
Median (IQR)	2.3 (0.53-9.4)
First ART regimen	
Nevirapine based	1134 (87)
Efavirenz based	168 (13)
History of chronic co-morbidities*	
Yes	292 (14)
No	1854 (86)
Socioeconomic status	
Low	594 (34)
Middle	544 (32)
High	588 (34)
*Comorbidities included hypertension, diabetes, TB, and cancer. SD=standard deviation, IQR=interquartile range	

Table 7: Treatment Adherence, interruptions levels and reasons for missed doses

Adherence outcome	Percentage (All visits)	Percentage (patients)
Missed dose in the past 3 days	3.5 (326/9281)	4.5 (93/2056)
Not Missed	94.3 (8749/9281)	
One day	2.2 (202/9281)	
Two days	0.87 (81/9281)	
Three days	0.46 (43/9281)	
Not known	2.2(206/9281)	
Missed dose in the previous month	9.1 (837/9237)	9.0 (190/2121)
Not missed	93.1(8597/9237)	
Last week	1.26 (116/9237)	
1-2 weeks	1.29(119/9237)	
2-4 weeks	3.8 (348/9237)	
Not known	0.8 (7/9237)	
Combined missed dose	9.9 (922/9231)	12.5 (265/2123)
Treatment interruption (days)*	(15.5:7-90)	8.8 (189/2146)
Reasons for missed dose		
Forget		48(199/411)
Ran out of pills		19(77/411)
Away from home		17 (68/411)
Too ill		7(30/411)
Others		9(37/411)
*The denominator of treatment interruption was no of participants because the question was about adherence in the previous year, (Med:IQR)		

Table 8 Univariate and multivariate logistic regression models of non-adherence

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	CI	P-value
Sex						
Female	0.96	0.80-1.14	0.615	1.03	0.79-1.35	0.809
Marital status						
Married/Cohabiting	Ref			Ref		
Never married	1.10	0.86-1.29	0.622	1.02	0.75-1.40	0.900
Separated/Widowed	1.00	0.79-1.23	0.881	1.01	0.73-1.39	0.972
Socio-economic status						
High	Ref			Ref		
Middle	1.21	0.95-1.53	0.117	1.23	0.91-1.67	0.172
Low	1.23	0.97-1.55	0.089	1.29	0.95-1.74	0.095
Age in years (per 10 years)	0.93	0.88-0.99	0.020	0.96	0.88-1.06	0.441
Season						
Dry*	1.10	0.93-1.23	0.309	1.05	0.80-1.37	0.724
Duration under ART (year)	0.92	0.87-0.96	<0.001	0.86	0.81-0.96	0.007
Nevirapine/Efavirence						
Efavirenz based	0.82	0.63-1.05	0.115	0.79	0.59-1.06	0.111
WHO clinical staging						
Stage III and IV	0.99	0.84-1.17	0.914	1.07	0.85-1.38	0.566
Ever changed ART						
Yes	1.21	0.96-1.51	0.102	0.98	0.66-1.43	0.908
Travel distance to the CDCI						
More than 5 km	0.95	0.80-1.14	0.529	0.79	0.61-1.02	0.082
Alcohol drinking						
Yes	0.99	0.81-1.20	0.888	1.18	0.88-1.57	0.267
Smoking						
Yes	0.94	0.73-1.22	0.657	0.72	0.48-1.09	0.122
Functional status						
Ambulatory/Bedridden	2.05	0.88-4.79	0.060	1.46	0.27-7.73	0.660
History of comorbidities**						
Yes	1.00	0.76-1.30	0.977	0.75	0.47-1.18	0.215
Time on study+						
No of interviews	0.93	0.89-0.97	0.002	0.82	0.70-0.97	0.024

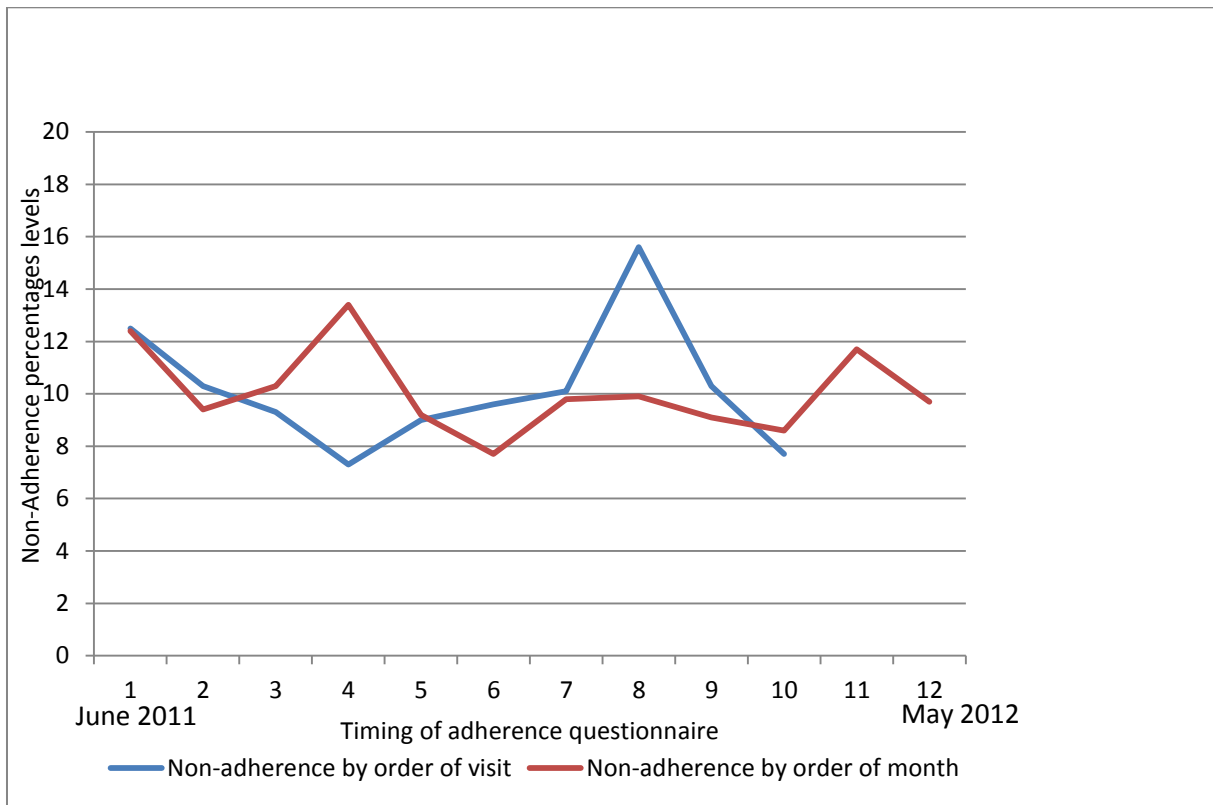
*Dry months are from May to December, **comorbidities include Hypertension, TB, Cancer or diabetes, Ref: Reference, + square term included

Table 9: Univariate and multivariate logistic regression models of baseline predictors

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	CI	P-value
Sex						
Female	0.92	0.67-1.27	0.615	1.19	0.74-1.90	0.469
Marital status						
Married/Cohabiting	Ref			Ref		
Never married	1.04	0.73-1.47	0.834	0.91	0.54-1.53	0.712
separated/Widowed	0.85	0.58-1.26	0.422	0.71	0.41-1.23	0.221
Socio-economic status						
High	Ref			Ref		
Middle	0.91	0.57-1.44	0.680	0.84	0.41-1.23	0.500
Low	0.86	0.56-1.39	0.597	0.9	0.51-1.39	0.681
Age in years (10 years)	0.88	0.79-0.98	0.020	0.91	0.76-1.09	0.312
Travel distance to the CDCI						
More than 5 km	0.9	0.66-1.23	0.515	0.67	0.43-1.06	0.078
Alcohol drinking						
Yes	1.05	0.74-1.49	0.773	0.78	0.48-1.27	0.316
Smoking						
Yes	0.96	0.61-1.50	0.842	2.36	1.03-5.43	0.043
Functional status*						
Ambulatory/Bedridden	1.14	0.65-1.98	0.651	0.87	0.38-1.94	0.573
History of comorbidities**						
Yes	1.27	0.85-1.91	0.241	1.22	0.61-2.42	0.574

**comorbidities include Hypertension, TB, Cancer or diabetes, Ref: Reference,

Figure 3: Non-adherence by order and month of visits



APPENDIX 1 : ADHERENCE QUESTIONNAIRE



DESIGNATED DISTRICT HOSPITAL

1. Patient Name _____
2. NACP NO _____
3. Date of visit ____/____/____
4. Did you ever miss ARV dose in the past 3 days
 - (a) No
 - (b) One day
 - (c) Two days
 - (d) Three days
 - (e) Not known
5. Prior to the 3 days when did you last miss medication?
 - (a) Last week
 - (b) 1 – 2 weeks
 - (c) 2 – 4 week
 - (d) Never skipped a medication
 - (e) Not known
6. Have you ever stopped medication in the past year ^(q)?
 - (a) Yes if yes for how long? _____
 - (b) No
7. Reason for missing ARV medication
 - (a) Toxicity
 - (b) I just forgot
 - (c) Share with others
 - (d) Stock out
 - (e) Felt better
 - (f) Too ill
 - (g) Ran out of pills
 - (h) Stigma
 - (i) Alcohol
 - (j) Influenced by someone else not to take the drug
 - (k) I felt depressed
 - (l) Too many pills
 - (m) I was away from home
 - (n) I was busy with other things
 - (o) Refused to answer
 - (p) don't know
 - (q) Other: Mention
8. Which facility did you last visit to take your medication?

9. (i) Have you ever Change/substitute ARV since you started?
 - (a) Yes (if yes then go to Qn. 10)
 - (b) No
10. Date of ARV change
 - (a) Change 1. Date ____/____/____
 - (b) Change 2. Date ____/____/____
 - (c) Change 3. Date ____/____/____
11. Reasons for change in drug
 - (a) TB or adverse reactions.
 - (b) Treatment failure
 - (c) Poor adherence
 - (d) Pregnancy
 - (e) End of PMCT
 - (f) Stock out
 - (g) Patient decision
 - (h) Others _____
12. Interviewer code ________

^(q) this question was added on 15/12/2011

APPENDIX 2: SOCIO-ECONOMIC STATUS QUESTIONNAIRE

1. Date of interview	
2. Nacp No	
3. Name of the patient	
What is the main source of drinking water for your family?	<input type="checkbox"/> 01. Piped Water into dwelling/yard/plot <input type="checkbox"/> 02. Shared tap/stand pipe <input type="checkbox"/> 03. Public tap / stand pipe <input type="checkbox"/> 04. Tube well/borehole <input type="checkbox"/> 05. Protected dug well <input type="checkbox"/> 06. Protected spring <input type="checkbox"/> 07. Rain water <input type="checkbox"/> 08. Unprotected dug well <input type="checkbox"/> 09. Unprotected spring <input type="checkbox"/> 10. Tanker truck/cart with small tank <input type="checkbox"/> 11. Surface water <input type="checkbox"/> 88. Don't know
Who is your main water provider?	<input type="checkbox"/> 1. Authority <input type="checkbox"/> 2. Community Based Organization/ Non Governmental Organization <input type="checkbox"/> 3. No provider <input type="checkbox"/> 8. Don't know
How long does it take you to go get water and come back?	Mins: <input type="checkbox"/> 2. On premise <input type="checkbox"/> 8. Don't know
What kind of toilet facility do members of your household usually use?	<input type="checkbox"/> 1. Flush or pour flush toilet <input type="checkbox"/> 2. Ventilated Improved Pit latrine (VIP) <input type="checkbox"/> 4. Traditional pit latrine <input type="checkbox"/> 5. No facility/bush/field <input type="checkbox"/> 6. Other:
Do you share this toilet facility with other households?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
Does your household have:	
Electricity?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A paraffin lamp?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A radio?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A television?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A mobile telephone?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A non-mobile telephone (landline)?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
An electric or charcoal iron?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A refrigerator?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
What type of fuel do you use the most in your household for cooking?	<input type="checkbox"/> 01. Electricity <input type="checkbox"/> 02. Bottled gas <input type="checkbox"/> 03. Paraffin/ Kerosene <input type="checkbox"/> 04. Charcoal 85 <input type="checkbox"/> 05. Firewood

	<input type="checkbox"/> 06. Crop residuals, straw, grass <input type="checkbox"/> 07. Animal dung <input type="checkbox"/> 08. No food cooked in household <input type="checkbox"/> 66. Other:
What is the main source of lighting in the household?	<input type="checkbox"/> 01. Electricity <input type="checkbox"/> 02. Solar <input type="checkbox"/> 03. Gas <input type="checkbox"/> 04. Paraffin hurricane lamp <input type="checkbox"/> 05. Paraffin pressure lamp <input type="checkbox"/> 06. Paraffin wick lamp <input type="checkbox"/> 07. Firewood <input type="checkbox"/> 08. Candles <input type="checkbox"/> 09. Other:
What is the main material on your floor?	<input type="checkbox"/> 01. Earth/Sand/Dung <input type="checkbox"/> 02. Wood planks, bamboo, palm <input type="checkbox"/> 03. Parquet or polished wood <input type="checkbox"/> 04. Vinyl or asphalt strips <input type="checkbox"/> 05. Ceramic tiles, terrazzo <input type="checkbox"/> 06. Cement <input type="checkbox"/> 07. Carpet <input type="checkbox"/> 08. Other: <input type="checkbox"/> 88. Don't know
What is your wall made of?	<input type="checkbox"/> 01. Grass <input type="checkbox"/> 02. Poles and mud <input type="checkbox"/> 03. Sun dried bricks <input type="checkbox"/> 04. Baked bricks <input type="checkbox"/> 05. Wood/ timber <input type="checkbox"/> 06. Cement blocks <input type="checkbox"/> 07. Stones <input type="checkbox"/> 08. Other: <input type="checkbox"/> 88. Don't know
What is your roof made of?	<input type="checkbox"/> 1. Grass/thatch/mud <input type="checkbox"/> 2. Iron sheets <input type="checkbox"/> 3. Tiles <input type="checkbox"/> 4. Concrete <input type="checkbox"/> 5. Asbestos <input type="checkbox"/> 6. Other: <input type="checkbox"/> 8. Don't know
How many rooms in your household are used for sleeping?	No. of rooms:
Does any member of your household own:	
A watch?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A bicycle?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A motorcycle?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A car or a truck?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
A bank account?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes <input type="checkbox"/> 8. Don't know
Did you worry that your household would not have enough food?	<input type="checkbox"/> 0. No -> go to question 72 <input type="checkbox"/> 1. Yes-> go to question 71 <input type="checkbox"/> 8. Don't know
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know
Was there any time when you or any of your household members could not eat the food you wanted because you	<input type="checkbox"/> 0. No -> go to question 74 <input type="checkbox"/> 1. Yes-> go to question 73 <input type="checkbox"/> 8. Don't know

didn't have resources?	
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know
Was there ever a time when you or a household member had to eat a limited variety of foods due to a lack of resources?	<input type="checkbox"/> 0. No -> go to question 76 <input type="checkbox"/> 1. Yes-> go to question 75 <input type="checkbox"/> 8. Don't know
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know
Did you or a household member have to eat some foods that you didn't want to eat because of lack of resources to obtain other foods?	<input type="checkbox"/> 0. No -> go to question 78 <input type="checkbox"/> 1. Yes-> go to question 77 <input type="checkbox"/> 8. Don't know
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know
Did you or a household member ever compromise on the portion of food you ate because there was not enough?	<input type="checkbox"/> 0. No -> go to question 80 <input type="checkbox"/> 1. Yes -> go to question 79 <input type="checkbox"/> 8. Don't know
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know
Was there any point where you or your household member had no food in the household because of lack of resources?	<input type="checkbox"/> 0. No -> go to question 82 <input type="checkbox"/> 1. Yes -> go to question 81 <input type="checkbox"/> 8. Don't know
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know
Did you or a household member sleep hungry at night because of food shortages in the house?	<input type="checkbox"/> 0. No -> go to question 84 <input type="checkbox"/> 1. Yes -> go to question 83 <input type="checkbox"/> 8. Don't know
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know
Did you or a household member go hungry in day and night because of limited food in the house?	<input type="checkbox"/> 0. No <input type="checkbox"/> 1. Yes -> go to question 85 <input type="checkbox"/> 8. Don't know
How often did this happen?	<input type="checkbox"/> 1. Rarely (1 – 2 times in the last 4 weeks) <input type="checkbox"/> 2. Sometimes (3 – 10 times in the last 4 weeks) <input type="checkbox"/> 3. Often (More than 10 times in the last 4 weeks) <input type="checkbox"/> 8. Don't know

Source: Questions taken from 'ICC Form 3'

CHAPTER SIX: ART resistance mutations in rural Tanzania: children and adolescents carry a heavy burden

ABSTRACT

Background

Due to the limited access to second and third line therapy regimens in resource limited settings, the extended preservation of first line drugs is currently essential for better treatment outcomes among patients on ART. This study aimed at estimating the level of treatment failure and viral resistance. In addition we set out to identify demographic and clinical factors associated with the occurrence of resistance related mutations during ART.

Methods

A cross-sectional study targeted 163 patients of all clinical staging and aged above two years who have been taking ART for at least six months. The study was done in a rural HIV clinic located in Tanzania. We assessed genotypic drug resistances by nucleotide sequencing and the Stanford HIV drug resistance database Version 6.2.0. Treatment failure to ART (defined as having a viral load of >100 copies/mL) and resistance mutations were expressed in proportions. Univariate logistic regression was used to identify predictors of genotypic ART resistance.

Results

Out of 163 study participants, 12% were younger than 18 years. 62% received D4T+3TC+NEV as their first ART regimen, 69% were in WHO clinical staging I and II and mean time on ART was 3.7 years. The level of treatment failure was 5.5% (9/163). Eight of these failures had at least one treatment-relevant mutation by genotypic analysis. The overall rate of genotypic resistance to ART was 4.9% (8/163). The proportion of treatment-relevant mutation was higher among younger participants 31.6% (6/19) than among adults 1.4% (2/144).

Conclusion

The rate of genotypic resistance to ART was low (<5%) and the burden of resistance associated mutations was highest in participants under 18 years. This study underlines the importance of viral genotyping as a monitoring tool for HIV patients.

BACKGROUND

An estimated 35.3 million [32.2–38.8 million] people were living with HIV at the end of 2013. According to UNAIDS, 3.3 million children had HIV globally, 2.9 million in sub-Saharan Africa (UNAIDS, 2013c). By reducing HIV viral load and restoring immune function, ART has led to substantial reductions in HIV-attributable morbidity and mortality and has greatly improved the quality of life for people living with HIV. The ART coverage in low and middle-income countries represented only 34% (32-37%) of the 28.6 million patients who were eligible in 2013 (UNAIDS, 2013a). The public health approach to scaling up ART in resource-limited settings involves the use of standardized treatment regimens (National Aids Control programme, 2005). The approach allows providing services out of specialized centres, standardizing ART regimen and using immunological and clinical definitions to monitor HIV patients. The public health approach is less sensitive to predict virologic failure, especially in children (Emmett et al., 2010) and thus patients experience increased durations of unsuppressed viremia compared to those monitored with viral load elsewhere (Barth et al., 2011).

ART resistance is a cause and a consequence of treatment failure among HIV patients on treatment (Clavel & Hance, 2004; Tang & Shafer, 2012). The absence of a virologic response after ART initiation may indicate transmitted treatment-related resistant mutations (Little et al., 2002). In resource-limited settings, first-line ART for HIV-positive patients consists of a triple combination of nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs). In such settings, protease inhibitors (PIs) usually form the core component of second-line therapy (Elliott et al., 2008).

Chronic disease clinic Ifakara (CDCI) is a care and treatment clinic located in Ifakara town in Kilombero district and has providing outpatient services to HIV positive patients since 2005. It aims to implement care and treatment for HIV/AIDS patients according to the Tanzanian national AIDS control programme (NACP, 2008b).

We estimated virological treatment failure and viral genotypic resistance to ART and investigated demographic and clinical factors associated with treatment-relevant mutations.

METHODS

Study design and enrollment

A cross-sectional study was performed on patients aged > 2years who had been on ART for more than six months. We enrolled patients who on ART who attended the Chronic Disease Clinic Ifakara (CDCI) in June 2013 during a routine visit, have been on ART for more than six months and willing to participate in the study. Patients who were critically ill and those with no post-ART plasma sample available were excluded from the study.

Treatment initiation at CDCI

During the study period, all patients with CD4⁺ cell count <350 cells/μL, patients with WHO stage IV regardless of CD4⁺ cell count, and pregnant women with WHO stage III or IV regardless of CD4 count were eligible to start ART (WHO, 2010b). Additionally, patients were required to come to the clinic with an adherent assistant who will help the patients to take their ART correctly. After treatment initiation patients had to adhere to scheduled clinical and drug refill visits.

Study settings

The study was conducted within the ongoing observational HIV cohort, Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), at the CDCI in St Francis Referral Hospital (SFRH). The CDCI has been providing ART in Ifakara since 2005 (Mossdorf, Stoeckle et al., 2011; Mossdorf, Stoeckle et al., 2010; Stoeckle, McHomvu et al., 2006) in accordance with guidelines of the Tanzanian National AIDS Control Program (NACP) (National Aids Control programme, 2005). All patients signed a written consent.

Study conduct and outcome

Viral load was performed on all participants recruited in the study. Those patients with >100copies/mL of RNA in their plasma sample were regarded as treatment failure.

Individuals with treatment failure were eligible for a viral genotyping yielding a binary outcome (with or without treatment-related mutation). The outcome was defined as presence or absence of ART resistance-associated mutations.

Laboratory methods

Blood sampling /volume/ storage:

Blood samples (10-20ml) were obtained from participants during scheduled laboratory monitoring or when a physician requested the samples for taking urgent clinical decisions. The samples were then stored at -80°C for clinical and research purposes. The blood was centrifuged to separate the cells and plasma

Sequencing

Plasma was isolated and frozen at -80°C until testing for viral load or drug resistance. Plasma HIV RNA was extracted using the Quigen kit (QIAamp[®] Viral RNA Kit) and quantified using the StepOne Real Time PCR system (Applied biosystem). For samples with detectable Viral Load, HIVDR genotyping was performed using the ABI Genetic Analyser (3130 Genetic Analyser) using an in-house PCR protocol. (<http://hivdb.stanford.edu>). We included all drug resistance mutations that conferred low, intermediate or high-level resistance. The consensus sequences were assessed for drug resistance mutations by using the Stanford University HIV Drug Resistance Database HIVdb program Version 6.2.0.

Viral load ascertainment

Viral load was determined with a One Step Real-Time PCR System (Applied Biosystems) by using a modification of the manufacturer's instructions. cDNA was synthesized as shown above, but using random primers (0.1 lg/l). The cDNA was then quantified by qRT-PCR. The qRT-PCR reaction contained 12.5 ll TaqMan Gene Expression Master Mix, 0.125 ll forward primer M2227F, 5'AGC CTC AAT AAA GCT TGC CTT G-3' (10 IM), 0.125 ll reverse primer M2228R, 5'-CGG GCG CCA CTG CTA G-3' (10 IM), 0.5 ll of probe HIV-FAM/BHQ with FAM as a reporter dye located at the 5' end and a black hole quencher at the

3' end, 5'-TGC CCG TCT GTT GTG TGA CTC TGG TAA-3' (10 IM), 5 µl cDNA, and RNase free water to a final 25 µl reaction volume. qRT-PCR thermocycling conditions were as follows: incubation (50°C, 2 min), initial denaturation (95°C, 10 min), and 44 cycles of denaturation (95°C, 30 sec and annealing and extension (60°C, 1 min). Quantification of cDNA was done relative to triplicate standard curves generated in each run from serial dilutions of a plasmid containing a viral DNA insert. Three “no template” controls were included for each run.

CD4⁺ T cells

A single platform technique (SPT) was used to enumerate CD4⁺ T-helper cells using BD TruCount tubes (BD Biosciences, San Jose, CA). EDTA whole blood was stained using 5 µl monoclonal antibody mixture BD TriTEST CD3- FITC/CD4-PE/CD8-PerCP (BD Biosciences) followed by 450µl BD lysis and fixative solution. Data acquisition and analysis by the MultiTEST software were performed using a three-color BD FACS Calibur (Becton Dickinson Immunocytometry Systems 2350).

Data management and analysis

Amino acids with mixed genotyping results (mutation plus wild type) were grouped with resistance associated mutations. The risk variables investigated were: sex, residence, CD4+ cell count (at the time of ART initiation), WHO clinical staging (at the time of ART initiation), age at ART initiation (binary: younger participants i.e. <18 years, older participants more than 18 years), duration under therapy (defined as difference between cART initiation and date of sample collection dates) and initial ART regimen. During analysis missing values were left to be missing. The level of treatment failure and ART mutations were analysed by descriptive techniques. Univariate Logistic regression was used to find determinants of ART genotypic resistance mutations. Only univariate analyses were performed owing to a low sample size.

Ethical considerations

The study was undertaken as part of the KIULARCO operational research (Mossdorf Erik, Marcel Stoeckle et al., 2011) which had received ethical and research clearance from the Ifakara Health Institute Institutional Review Board, the National Research Ethics Committee, Medical Research Coordination Committee of the National Institute for Medical Research (NIMR) through the Tanzania Commission for Science and Technology (COSTECH). All patients have given written consent before participating into the study. Patients with cART-related mutations had their drugs switched or changed to avoid a failing regimen.

RESULTS

Data characteristics

Among the 163 participants enrolled, 69.3% (113/163) were females, 12% (19/163) were <18 years old, 54.6% (89/163) resided within Ifakara town. At the time of cART initiation, the median CD4⁺ cells count level was 256.5cells/ μ L, 68.9% (112/163) were asymptomatic (WHO clinical stage I or II) and 62.4% (105/163) had d4T+3TC+NVP as their initial first line regimen. The mean duration on ART was 3.7 (0.4-7.8) years (Table 10).

Treatment failure and drug resistance strains to cART

Treatment failure to ART defined as a viral load >100 copies/mL, was observed in 5.5% (9/163) of participants. The median viral load among patients with treatment failure was 11343 copies/ml (IQR: 2010-22623). Of the nine patients with a detectable viral load, eight had at least one cART-related mutation. We found a total of 7 different NRTI, 11 NNRTI and 3 PI resistance-associated mutations. Among the seven different NRTI mutations there was only one major mutation (M184V) appearing in five patients representing 3.1% of the participants. According to the Stanford algorithm, there were six minor NRTI mutations namely L210W, V75M, T215Y, Y115F, M41L and L74I. Among the 11 different NNRTIs, the two major mutations (K103N (4 cases) and Y181C (1 case)) were found in six patients representing 3.7% of the participants. The nine minor NNRTI mutations were A98G, V108I,

K238T, V106M, H221Y, E138G, V90I, V179D and F227L. No major PI mutations among our participants were detected, however three minor treatment-related drug resistances were detected (L10I, L33F and T74S) as listed in Table 11.

Factors associated with resistance associated mutations

Among the eight participants who had at least one resistance-associated mutation, 62.5% (5/8) were females, 75% (6/8) were young participants, who had been on ART for an average 2.8 years (range: 1.2-4.6) as shown in Table 11. Overall, the rate of ART resistance associated mutations among younger participants was 31.6% (6/19) compared to 2.1% (3/144) in adults. The mean age of participants with and without treatment-related mutations was 16.7 years (95% CI 6.21-27.3) and 35.6 (95% CI 33.5-37.8) respectively. The association between age and resistance associated mutation was statistically significant ($p < 0.001$). In terms of the burden of mutations, younger participants carried 93% (14/15) of the detected NRTI mutations, 80% (16/20) of NNRTI mutations and 33.3% (1/3) of the PI mutations. The most prevalent NRTI resistance associated mutations (RAM) in participants <18 years of age were M184V (5/6) and Y115F (3/6). V75M and M41L were also detected in two patients under the age of 18 years. The most common NNRTI mutations in participants <18 years was K103N which confers resistance to efavirenz and nevirapine. K103N was identified in half (3/6) of the participants of whom all were under 18 years. Other common NNRTI mutations in this group were A98G (2/6), V108I (2/6), K238T (2/6) and Y188F (2/6). Only one minor PI mutation (L10I) was found among younger participants. Only one adult participant with an NRTI resistance mutation M184V was observed. Among adults with NNRTI mutations only one patient had K103N, V106IM, V179D and F227L and two patients had PI resistance mutations namely L33F and T74S.

The treatment failure rate among patients on cART for <2 years was 6.1% (2/33) compared to 5.3% (7/131) among patients with >2 years. Both patients who had been on cART for less than 2 years had M184V and K103N resistance associated mutations in common. The mean

duration of therapy with and without drug associated mutations was 2.8 and 3.8 years respectively. Two patients who had been on ART for > 3.7 years shared the following mutations: M184V, T215Y, M184V and K103N.

DISCUSSION

Our study found that the level of HIV drug resistance in CDCI patients under ART was around 5% and, most importantly, that a higher proportion of the burden is in children and teenagers. The higher rate of treatment-related resistance among younger participants might be explained by previous exposure to single dose nevirapine, suboptimal dosing and non-adherence to ART.

No sequencing information on pre-ART samples was available, which makes it difficult to know if the resistance mutations were transmitted or not. For these children with treatment-related resistances, there was no mother-child pair and no prior information on pre-delivery ART exposure thus linking treatment-related mutations to previously ART exposure was impossible.

A high prevalence of drug-associated mutations after treatment failure has been reported in previous studies. A study done on patients from the TREAT Asia Studies to Evaluate Resistance-Monitoring study (TASER-M), found 92% of patients who failed first line drugs harbor treatment-related mutations (Jiamsakul, Sungkanuparph, et al., 2014). If treatment-related mutations are not detected during therapy, they will eventually accumulate and dilute the effectiveness of the drug in use.

In comparison to an earlier study conducted in the same setting in 2007 (Masimba, Kituma et al., 2013), the rates of treatment-related resistances seems to have changed. The proportion of major NRTI mutations has increased from 1.7% to 3.1% while that of NNRTI has slightly increased from 3.3% to 3.6%. The proportion of PIs mutations has dropped sharply from 5.8% in 2007 to 1.8% in 2013. The reasons for these changes might be partly contributed by the fact that the previous study enrolled only HIV clients above the age of 18 years. The

increase of NRTI mutations might be attributed by suboptimal drug levels contributed by non-adherence to therapies and unplanned treatment interruptions. Previous studies in other countries have shown that younger HIV positive clients have higher rates of non-adherence compared to adults (Bygrave et al., 2012; Evans et al., 2013; Nachega et al., 2009).

The sharp drop in PIs resistance mutation might be explained by the fact that the younger participants were not exposed to the protease drug. The PIs are well known by their potency and high genetic barrier to resistance (Wainberg & Friedland, 1998). The study has found several thymidine analogue mutations (TAMs) as expected in resource limited settings where TAMs analogues are prescribed as first line therapy (Jiamsakul, Sungkanuparph et al., 2014). TAMs originally selected by zidovudine and stavudine confer reduced susceptibility to all NRTIs (Jiamsakul, Sungkanuparph et al., 2014). Mutation M184V which was found in five patients, causes high-level resistance to lamivudine and emtricitabine and low-level resistance to didanosine and abacavir. Resistance to abacavir increases if M184V occurs together with other TAMs (V. A. Johnson et al., 2013; Praparattanapan, Kotarathitithum et al., 2012; Shafer et al., 2008) associating with multi-NRTI drug resistance (V. A. Johnson, Calvez et al., 2013). This could become serious problem in Tanzania since NRTIs are widely used as a backbone to both first and second line drugs. The absence of more complex mutational patterns, conferring broad cross-resistance to most NRTIs in these findings, suggesting a controllable situation as NRTI is a backbone to first and second ART regimens. Currently resistances to NNRTIs are of particular concern in resource limited settings because this drug class forms the basis of all first line treatment regimens as well as for prevention of mother to child transmission (Wainberg et al., 2011; WHO, 2010a). The slight increase in NNRTI mutations among our participants might be partly explained by the exposure single dose nevirapine to pregnant mothers (McConnell et al., 2007), low adherence among younger participants as noted in previous studies (Bygrave, Mtangirwa et al., 2012; Evans, Menezes et al., 2013;

Nachega, Hislop et al., 2009). NNRTIs have low genetic barrier and thus require excellent adherence to avoid resistances to occur.

Single-dose NVP can favor the selection of HIV-1 resistant mutants in mothers and infants. ART was available to a limited number of individuals since 1996 in Tanzania as mono and dual therapies (Kasang, Kalluvya et al., 2011; G. R. Somi, Kibuka et al., 2008) and single dose nevirapine was given to HIV pregnant women few weeks before delivery to prevent vertical transmission (NACP, 2008b) from 2004 to 2010. Similarly, treatment-related resistant virus emerged as experienced in countries which were the first to introduce mono and dual ART therapies resistance (Grant et al., 2002; Little, Holte et al., 2002; Wensing et al., 2005). Due to lack of data we could not associate previous ART exposure and genotypic resistances.

Non-adherence among younger participants may partly explain the burden of resistance associated mutations in younger participants. Earlier reports have shown poorer adherence in adolescents compared to adults (Bygrave, Mtangirwa et al., 2012; Evans, Menezes et al., 2013; Nachega, Hislop et al., 2009) or to younger children (Lowenthal et al., 2014). On the other hand, in an analysis of the determinants of adherence to cART among HIV-infected patients in Côte d'Ivoire, it was reported that 10% of interruptions were related to drug stock-outs (Diabate S et al., 2007). Accumulation of treatment-related mutations may be fueled by limited access to monitoring of plasma viral load to detect treatment failure much earlier than the current public health approach (Hosseinipour et al., 2009; Sigaloff et al., 2011).

Our study indicated that younger participants are at an increased risk of harboring drug resistance mutations compared to adults. Timely actions are called for to design ways for early detection and control of drug resistance mutations. More studies are needed to understand the links between younger age and presence of treatment related mutations.

In conclusion, the association between children and HIV drug resistance needs further research on what might have caused a higher proportion of children to bear the burden so as to find appropriate solutions.

Table 10: Participants characteristics (n=163)

Variables	Overall (163)	Children and adolescents (19)	Adults (144)
	n (%)	n (%)	n (%)
Sex			
Male	50 (30.7)	9 (47.4)	41 (28.5)
Female	113 (69.3)	10 (52.6)	103 (71.5)
Marital status			
Ever married	114 (71.3)	3 (17.7)	111 (78.2)
Never married	46 (28.7)	15 (83.3)	31 (21.8)
Residence			
Ifakara town	89 (54.6)	7 (36.8)	82 (56.9)
Outside Ifakara town	74 (45.4)	12 (63.2)	62 (43.1)
Initial ART regimen			
D4T+3TC+NEV	105 (62.4)	15 (79.0)	90 (62.5)
D4T+3TC+EFA	24 (14.7)	1 (5.3)	23 (16.0)
AZT+3TC+NEV	4 (2.5)	2 (10.4)	2 (1.4)
AZT+3TC+EFA	19 (11.7)	1 (5.3)	18 (12.4)
TDF+FTC+EFV	2 (1.2)	0 (0.0)	2 (1.4)
Others	9 (5.5)	0 (0.0)	9 (6.3)
WHO clinical staging			
Stage 1	61 (37.4)	5 (26.3)	56 (38.9)
Stage 11	51 (31.3)	10 (52.6)	41 (28.5)
Stage 111	40 (24.5)	4 (21.1)	36 (25)
Stage 1V	11 (6.8)	0 (0)	11 (7.6)
CD4			
<350 cells/mm ³	107 (65.6)	10 (52.6)	97 (67.4)
>350 cells/mm ³	56 (34.4)	9 (47.4)	47 (32.6)
Time on ART			
6-12 months	7 (4.3)	0 (0)	7 (4.9)
12-24 Month	25 (15.3)	3 (15.8)	22 (15.3)
>24 months	131 (80.4)	16 (84.2)	115 (79.9)
Viral load			
>100 copies/mL	9 (5.5)	6 (31.6)	3 (2.1)
<100 copies/mL	154 (94.5)	13 (68.4)	141 (97.9)
RAM			
>100 copies/mL	9 (5.5)	6 (31.6)	3 (2.1)
<100 copies/mL	154 (94.5)	13 (68.4)	139 (97.9)

Table 11: Predictors of resistance mutations to ART

Variables	ART mutation rates		Logistic regression	
	No mutation (n, %)	Mutation (n, %)	OR (95% CI)	P-Value
Sex				
Male	47 (94)	3 (6)	1	
Female	107 (95.5)	5 (4.5)	0.88 (0.21-3.66)	0.859
Residence				
Ifakara town	84 (94.4)	5 (5.6)	1	
Outside Ifakara town	70 (95.9)	3 (4.1)	0.96 (0.25-3.70)	0.953
Age				
Adults	141 (98.2)	2 (1.4)	1	
Children	13 (68.4)	6 (31.6)	21.7 (4.9-97.0)	<0.001
Initial ART regimen				
D4T containing regimen	123 (96.1)	5 (3.9)	0.50 (0.12-2.13)	0.343
Others*	31 (91.2)	3 (8.8)	1	
WHO clinical staging#				
Stage I	58 (96.7)	2 (3.3)	-	
Stage II	46 (90.2)	5 (9.8)	-	
Stage III	39 (97.5)	1 (2.5)	-	
Stage IV	11 (100)	0 (0)	-	
CD4+ cell count				
<350 cells/mm ³	103 (96.3)	4 (3.7)	1	
>350 cells/mm ³	51 (92.7)	4 (7.3)	2.5 (0.64-9.8)	0.181
Time on ART (months)				
6-24	30 (92.8)	2 (6.3)	1	
>24	124 (95.4)	6 (4.6)	0.85 (1.7-4.3)	0.841
Viral non-response				
No	154 (100)	0 (0)	-	-
Yes	0 (0)	8 (100)		
*AZT+3TC+NEV, TDF+FTC+EFV				
# The limited numbers did not permit meaningful categories for the regression				

Table 12: Distribution of Resistance associated mutations by age

Mutation type	ALL (38,100)		Children (31,100)		Adults (6,15)			
NRTI	M184V	5 (33.3)	M184V	4 (28.6)	M184V	1 (100)		
	L210W	2 (13.3)	L210W	2 (14.3)				
	V75M	2 (13.3)	V75M	2 (14.3)				
	T215Y	2 (13.3)	T215Y	2 (14.3)				
	M41L	2 (13.3)	M41L	2 (14.3)				
	Y115F	1 (6.7)	Y115F	1 (7.1)				
	L74IL	1 (6.7)	L74IL	1 (7.1)				
	Column % Row %	Subtotal	15 (39.5)	Subtotal	14 (45.2) Subtotal	14 (93.3)	Subtotal	1 (16.7) Subtotal
NNRTI	K103N	5 (25)	K103N	4 (25)	K103N	1(25)		
	A98G	2 (10)	A98G	2 (12.5)	V106M	1 (25)		
	V108I	2 (10)	V108I	2 (12.5)	V179D	1 (25)		
	K238T	2 (10)	K238T	2 (12.5)	F227L	1 (25)		
	V106M	2 (10)	V106M	1 (6.3)				
	H221Y	1 (5)	H221Y	1 (6.3)				
	E138G	1 (5)	E138G	1 (6.3)				
	Y181C	1 (5)	Y181C	1 (6.3)				
	V90I	1 (5)	V90I	1 (6.3)				
	V179D	1 (5)	P225H	1 (6.3)				
	F227L	1 (5)						
	P225H	1(5)						
	Column % Row %	Subtotal	20 (52.6)	Subtotal	16 (51.6) Subtotal	16 (80)	Subtotal	4 (50) Subtotal
PI	L10I	1 (33.3)	L10I	1 (100)	L33F	1 (50)		
	L33F	1 (33.3)			T74S	1 (50)		
	T74S	1 (33.3)						
Column % Row %	Subtotal	3 (7.9)	Subtotal	1 (3.2) Subtotal	1 (33.3)	Subtotal	2 (33.3) Subtotal	2 (66.7)

Table 13: ART history by age

ART History	Children	Adults
	n (%)	n (%)
D4T+LAM+NEV	216 (35.6)	35 (47.3)
D4T+3TC+EFA	126 (20.8)	12 (16.2)
AZT+3TC+NEV	8 (1.3)	1 (1.4)
AZT+LAM+EFA	57 (9.4)	9 (12.2)
TDF+FTC+EFV	55 (9.1)	2 (2.7)
TDF+FTC+NVP	4 (0.7)	0 (0)
123	53 (8.0)	1 (1.4)
ABC+DDL+LPV/R	24 (4.0)	3 (4.1)
ABC+DDI+NFV	15 (2.5)	1 (1.4)
TDF+FTC+LPV/R	24 (4.0)	4 (5.4)
ABC+3TC+LPV/R	5 (0.8)	1 (1.4)
OTHER2NDLINE	13 (2.2)	4 (5.4)
TDF+3TC+LPV/R	1 (0.2)	1 (1.4)
OTHERS	5 (0.8)	0 (0)
*Missing data		

CHAPTER SEVEN: Discussion and conclusion

We studied the barriers to successful ART programmes in a resource limited setting. Six years after the free ART programme was introduced in Tanzania, issues of access, adherence and ART resistance are still of concern. The objectives of the project were to understand the supply chain of HIV rapid tests, cotrimoxazole and ART in rural settings; to estimate levels and determinants of ART non-adherence and to find predictors of ART resistance-associated mutations among HIV positive patients on treatment. Below, we synthesize the study results and discuss policy adaptations and programme actions that might address the problems identified. Limitations of the study design are discussed, as are potential future research activities that could fill the gaps identified in this project.

The study shows that despite ART decentralization, critical issues in patient management, such as stock-outs, need to be addressed. Children and adolescents presented with lower adherence rates compared to other participants on ART. This is due to caretaking issues, HIV stigma and poverty. In the resistance study, children were shown to be more prone to ART genotypic resistances compared to adults. Stock-outs of CTC supplies were evident around Kilombero and Ulanga districts in the supply chain paper (chapter three), yet they were not reflected directly in the subsequent adherence and resistance studies. Non-adherence was attributed, not to stock-outs, but to non-parental caretakers, proximity of CDCI and difficult economic experiences. If resistance had been a consequence of stock-outs, all age groups would have been affected with ART genotypic resistances in the same proportion. Instead, stock-outs were controlled in the CDCI to the extent that it did not contribute to non-adherence. We are not aware of the status of stock-outs in the peripheral CTCs since the study on situational assessment supplies ended.

ART non-adherence is associated with several risk factors, but living in poverty is common among all such cases. Apart from poverty, the study on children showed that living with a

non-parental caretaker and HIV stigma were associated with non-adherence. The other adherence study showed newer ART users and patients residing close to the clinic were at risk of non-adherence. These findings reveal the different struggles that patients of different ages face while on ART. It is widely known that children's adherence levels rely heavily on the caretakers assigned to them (Steele, Nelson et al., 2007). When a non-parental caretaker is assigned to be a new adherent assistant to the child, he/she might not be aware of ART's benefits and/or lack experience to play new role. He/she may not assist the patient to take drugs as usual or may even overdose the child with ART. New ART users may be subjected to the stigma that surrounds HIV disease and must also get used to ART side effects at the beginning of the therapy. The difference in risk factors for adherence among different age and patient groups is a signal that intervention studies to improve ART adherence should focus on these specific factors to effectively address the problems to enable better treatment outcomes.

Participants in both adherence studies reported non-adherence to ART, with children reporting lower adherence compared to adults. This paradox was reflected in the ART genotypic resistance study (chapter six), as a larger proportion of children and teenagers had genotypic resistance associated mutations than did the adults. Future studies are needed to investigate why children are more likely to acquire ART resistance compared to adults.

There is little evidence from intervention studies, to show that addressing major barriers improves adherence among vulnerable groups such as children and adolescents (Scanlon et al., 2013). Studies looking at the effect of food provision and HIV disclosure on adherence have yielded positive results (Bikaako-Kajura, Luyirika et al., 2006). Disclosing a child's HIV status is important for long-term disease management and is associated with improved adherence and reduced conflict with caregivers (Fetzer et al., 2011). ART programmes should consider the best ways to inform the child or potential caretakers of the child's HIV status and ensure that clinics implement the practice. Studies providing food to HIV patients in need

have found that HIV disclosure improves adherence (Cantrell et al., 2008). An intervention study focussing on the effects of food supplements could be helpful if it targets children and adolescents faced with food insecurity.

Having assessed and analysed information on the assessment of supply chain of HIV test kits, cotrimoxazole and ART, adherence and ART resistance, we suggest incorporating the following ideas into policy and strategic plans to improve ART management in Tanzania: The Global Fund report (The Global Fund, 2011) identified weak forecasting and lengthy procurement processes as the main factors behind antiretroviral drug stock-outs in African countries. Under-estimating of ART supplies may lead to stock-outs and may cause stress to patients and health workers (Supply Chain Management System, 2007). Likewise, over-estimating can put strains on storage space and may lead to wasting of drugs with limited shelf-life (Supply Chain Management System, 2006). There is a need for routine data collection on HIV test kits and drugs supplies to estimate the real demand and to enable timely ordering of ART items. This method of linking data systems with supply decisions was found to be successful in Malawi (Harries et al., 2007). At the programme level, routine data collection on HIV test kit and drug supplies can be used to reliably forecast needs and thus prevent stock-outs. To ensure cost-effectiveness, correctly estimating the necessary quantity of drugs is important. Ensuring there are no pauses in ART supplies, requires a stable supply of antiretroviral drugs from the source to the treatment centres.

Avoiding interruptions in ART supplies requires a stable supply of antiretroviral drugs from the source to the treatment centres. Transportation activities within the supply chain should include delivery tracking and must account for potential climate conditions. If the clinic is without power supply, installing a solar power system would enable data to be entered in a timely fashion to help with proper estimations. CTCs should adopt clear and reliable ways of conveying information to ART clients during stock-out periods and advise on exactly what patients should do and/or where to go. A proper tracking system for patients referred to

another clinic can help to ensure that patients actually attend and refill their ART prescriptions at the clinic to which they were referred. Such procedures and practices would minimise treatment interruptions and loss to follow-up.

Adopting mobile-health services to report and order items from the supply source would improve ART supply chain management by ensuring timely transmission of data to the source centre. A lack of reliable and a fast communication tools makes tracking stock levels problematic, particularly in remote areas. Short message service (SMS or text messaging) has been used to improve drug supply chain management in Kenya and Tanzania. Text messaging was used to provide real-time updates on drug stocks in health facilities, reducing stock-outs and supporting drug stock management (Barrington et al., 2010; Githinji et al., 2013). In developing countries, cellular telecommunication networks and mobile phones have increased coverage reaching 79% in 2011 (ICT Indicators database, 2011) making it easier to capitalize on and apply the technology. The tool is only effective when transport and communication systems can accommodate needs and deliver the required items in time. The ministry of health should collaborate with the telecommunication sector in order to agree on terms payment arrangements, thereby removing the burden and inconvenience to the CTCs. At the same time, the health system should monitor and communicate expired drugs or drugs that are about to expire so as to enable early redistribution of the drugs among nearby facilities. The system should budget for incentives for staff responsible for stock management and later assigned people to do the work under normal circumstances as it was done in the SMS for life pilot study (Barrington, Wereko-Brobby et al., 2010).

Extending ART management training to peripheral CTC staff, emphasising how to handle second line drugs and complicated cases at their sites, would be beneficial. Refresher training should also be available as changes in ART management arise, guided by informed decisions from ongoing research globally. Such training would enrich health care providers with sufficient and up-to-date ART knowledge and improve overall delivery of health services.

The World Health Organization estimates that the global shortage of trained health care staff exceeds four million (WHO, 2010c). For the suggested changes to work there must be a more political will, transparency in purchasing and distributing ART and frequent monitoring of health facilities by the district Council Health Management Team. (Wales, Tobias et al., 2014).

Ensuring optimal adherence levels is essential to avoiding the emergence of drug resistance. To detect resistance, low income countries like Tanzania would benefit from cheap tools to monitor viral load and genotyping sequencing at the district level. For example, a cheap mobile technology that uses recombinase polymerase amplification (RPA) to amplify DNA would be a boon in resource limited settings (Rohrman et al., 2015). At clinic level, adherence should be closely monitored and information gathered should be acted upon. Patients who do not respond to treatment should be directed for sequencing at a specified site.

The studies conducted and discussed in this work have brought to light important imbalances in ART management in Tanzania. They are, however, subject to some limitations. For example, in the assessment of supply study (chapter three), we did not interview staff from the drug source side, such as staff at the Medical Store Department (MSD) and the District Medical Officer (DMO). Thus, our analysis may have missed some other potential factors leading to delays in delivering orders to ART clinics or further issues surrounding stock-outs. In the adherence study on children and teenagers (chapter four), the decision to group a cohort 2–19 year olds together might have disguised specific adherence challenges for younger children (palatability, caregiver availability), which may be distinct from those for teenagers. Since participants aged 18 years and above made up less than 8% of the study population, it is unlikely to have biased our results. We capped the adherence limit at 100%; those above were categorized in the good adherence group. Technically, it may be argued that they were not good adherers as they took the drugs more than required and thus biasing our results in the direction of having many adherers while by strict definitions, they were not. In the second

adherence study (chapter five), the drop-outs were likely to have been non-adherers, given that non-adherence increases risk for mortality and lost to follow-up (LTFU). As a result, the group of long-term ART users is a biased selection of the better adhering patients. This study misses adherence information of clients who had defaulted from the clinic. In the ART resistance study (chapter six), we did not have data on previous ART exposure, which is an important explanation of genotypic resistance especially among children. This makes it difficult to ascertain the source of resistance mutations. Despite the study design shortcomings, the studies reveal important imbalances in ART management in Tanzania. The studies are internally valid, as they measure what was intended. Since some study components involved unannounced visits, all children on ART and followed patients over 12 months, we believe the data can be generalised to rural areas in SSA. The issues highlighted here may be a good starting point for improving ART management in the rural Tanzania and other rural areas in SSA with similar experience.

Gaps in our knowledge remain and should be reconciled through future research on ART. Potential areas to be explored include another operational study on assessing the ART supply chain, intervention studies to improve adherence, understanding the role of distance to the clinic on non-adherence, and establishing why children bear the burden of ART genotypic resistance. The study on assessing supply chain management showed stock-outs of ART supplies. However, the outcomes were not reflected in subsequent findings and it is important to establish why that is the case. As the status of ART supplies may change over time and neither our study nor the one done in Iringa (Layer, Kennedy et al., 2014) took into account the supply side (MSD), future studies that account for these factors would be valuable. The research question to be considered should be “An overall assessment of supply chain management of ART in peripheral settings”.

Findings on ART adherence among children (chapter four) show some patients took more drugs than required; it would be of interest to further investigate the dynamics of ART

overdose, its role in treatment interruptions and adverse clinical outcomes. Cases of ART overdose have been linked to having multiple caregivers (Kikuchi et al., 2014), suicide attempts (Krentz et al., 2005), prescribing errors (Commers et al., 2014) and use of unfamiliar language on the ART boxes (Iyaji et al., 2008). To our knowledge, there has not been a proper analytical study to investigate the problem among children and adolescents in Tanzania. The research questions suggested are “Predictors of ART overdose among children and adolescents in rural Tanzania”, “Impact of ART overdose in treatment interruption” or “comparing treatment outcomes among patient who overdose ART and those who do not”.

In the second adherence study (chapter five), we found an unexpected association between distance to the clinic and non-adherence. Our findings are consistent with those of Wakibi et al (Wakibi et al., 2011) who observed in Kenya that patients accessing therapy from ARV clinics within walking distance from their residence had poor adherence compared to those residing farther away. This warrants a qualitative study as neither study can properly explain the mechanism of the association. A research question to be considered should be “Why patients staying close to ART clinic fail to adhere to drugs: a qualitative study”.

There is a need for an intervention study to establish which intervention is best for helping ART patients who are struggling to maintain optimal adherence. Data on appropriate interventions to improve ART adherence in SSA, especially among children in SSA is limited. In 2009, Wamalwa et al showed that medication diaries did not improve ART adherence (Wamalwa et al., 2009). The same year, a study by Muller et al. followed patients using one of three different ART regimens; none of the interventions were superior in terms of adherence (Muller et al., 2009). A successful Community Based Adherence Support (CBAS) study in South Africa showed that the intervention did improve adherence and treatment outcomes (Fatti et al., 2014; Grimwood et al., 2012). None of these studies targeted stigma reduction towards HIV, followed patients for long periods of time or specifically target patients at risk of non-adherence (Fetzer, Mupenda et al., 2011).

One key to fighting stigma among HIV positive children could be educating their peers and influences. An ART education interventional study could target the people who spend the most time with the children, such as school mates and teachers, to find out if providing ART education improves the situation and change stigma to positive treatment support. To improve ART adherence among children, intervention studies should target HIV positive children at risk of missing their morning dose because of breakfast-dose timing. Based on our findings that children with non-biological caregivers have lower levels of adherence, usually because the assigned caregiver fails to remind the child to take medication, we suggest an intervention study that would target orphans and strengthen and motivate the assigned caretaker or recruit a community health worker who would be responsible for making sure these children take medication while at home (Direct Observed Therapy - DOT). The DOT programme has been highly successful in adherence to Tuberculosis therapy.

Our study on ART resistance showed that children and adolescents are most affected. Further investigations are needed to verify this finding in other rural settings and to consider why this is the case.

The studies we conducted over three years highlight important ART achievements, issues and research gaps. The findings serve as a basis from which to enrich ART management systems, through further investigation and action, in resource limited settings. While the ART programme in Tanzania is offered free of charge, HIV patients still incur substantial expenses in terms of transport and accommodation to reach and access ART clinics. The study further shows that patients from low economic status backgrounds struggle to maintain the required level of ART adherence. Shortcomings in the ART supply system need to be addressed to avoid stock-outs that lead to poor ART management and treatment outcomes. Discriminating against HIV positive individuals has been against the law in Tanzania since April 2008, yet it is still common. The stigma associated with HIV discourages some patients from adhering to ART. Children on ART face critical challenges when they are not informed of their illness

and when those assigned to assist children with their treatment do not do their job. Low levels of adherence have led to the emergence of ART genotypic resistance, occurring more frequently among children than among adults. We recommend further operational and analytical studies to better understand the findings and issues raised in our studies. Intervention studies are well suited to finding better ways of increasing ART adherence among children in resource limited settings.

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APPENDIX

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2007: DSS programme, **IHI-Data manager**

2003-2004: Mwadui Technical Secondary School-**Mathematics Teacher**

Conference Attended and workshop attended

2013: Europeans Aids conference-Brussels-Belgium

2012: Paedriatic conference –Dar-es-Salaam Tanzania

2012: International AID Conference-Washington-USA

July 2010: Longitudinal data management-Bagamoyo organized by IHI

June 23-July 11, 2008: Introduction to Longitudinal Data management and analysis. The University of the Witwatersrand school of public health in Collaboration with The University of Colorado Institute of Behavioural Science.

August 2007: Seminar on Global Information Systems (GIS). Institute of Health Research and Development Centre (IHRDC, now IHI) Ifakara-Tanzania

November 2006: Stata Software Workshop. Institute of Health Research and Development Centre (IHRDC) Ifakara-Tanzania

October 2006: Seminar for Good Governance. Mzumbe University Student's organization (MUSO).

Grants

2010: Global Fund round 8 through Health research users trust fund

PUBLICATIONS

ART at peripheral level: A situational assessment of Supply Chain Management in peripheral Care and Treatment Centres for HIV in rural Tanzania (**Published: Tanzania Journal of Health research**)

Predictors of non-adherence among children and adolescents in rural Tanzania (**accepted: BMC infectious disease**)