Challenges of continuum of HIV/AIDS care and treatment in Tanzania: the effects of parasites co-infections, HIV clinical manifestations, and adherence to antiretroviral therapy

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Dedicated to
All those who supported my education from 1973 to 2010.

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AZT	Zidovudine
CD4	T-lymphocyte Bearing CD4 Receptor
D4T	Stavudine
EFV	Efavirenz
HIV	Human Immunodeficiency Virus
MTCT	Mother to Child Transmission (of HIV)
NACP	National AIDS Control Program, Tanzania
NVP	Nevirapine
OI	Opportunistic Infection
PMTCT	Prevention of Mother to ChildTransmission (of HIV)
CI_{95}	95% Confidence Interval
CCR_5	Chemokine (C-C motif) Receptors
WHO	World Health Organization
3TC	Lamivudine
TDF	Tenofovir

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Summary

In Tanzania, the National AIDS Control Program with the support of Non-Government Organizations is scaling-up Antiretroviral Therapy (ART) services to peripheral (rural) health facilities.The aim of scaling-up is to improve availabilityaccess and adherence to ART by all HIV-infected population.

HIV-infected persons in peripheral (rural) areas are at increased risk for several medical co-morbidities including tuberculosis, bacterial and parasitic infections. As ART is successfully made universally available, non-AIDS co-morbidities caused by helminths and malaria will emerge as leading problems that will complicate care, adherence to ART and retention. These challenges can be improved by comprehensive and multidisciplinary management strategies. In addition a range of interventions such as counselling, use of treatment assist ants and integrated health services delivery need to be enhanced to improve adherence and treatment of co-morbidities.

However, concerns are raised regarding proper HIV/AIDS management in the peripheral (rural) settings which focuses on clinical monitoring and treatment of opportunistic infections. Clinical monitoring is based on WHO clinical st ages and CD4+ T-lymphocyte counts. Clinicians in the peripheral (rural) settings faces challenges in accessing CD4+ T-lymphocyte counts, HIV and AIDS clinical features not corresponding with WHO clinical stages, co-infections and co-morbidity.

The aim of the work reported in this thesis was to conduct research to investigate effects of concurrent parasites infections and challenges of HIV/AIDS case management on peripheral (rural) patients in order to contribute information towards better care for HIV/AIDS patients in Tanzania.

The studies were conducted at Tumbi Hospital and Chalinze Health Centre in Tanzania between April 2008 and June 2009. The research consisted of three sub-studies carried out consecutively utilizing different study designs and populations.

The first study examined the effects of parasite co-infection on CD4+ T-lymphocyte counts, WHO clinical staging and haemoglobin. In addition, the study attempted to develop a simplified clinical staging by utilizing local experiences HIV/AIDS clinical manifestation. Adult patients registering for the first time at HIV-clinic were clinically examined for malaria parasites and helminths. CD4 counts and haemoglobin were also analyzed. Patients were initiated on treatments according to their respective diagnosis and followed up for six months. At 6 months, clinical procedures were performed similar to first contact assessment.

The second study utilized a case-control design to elucidate factors associated with non-adherence to ART. Adult patients attending care and treatment at the study clinics and being on ART for at least three months were studied. Patients with ART adherence of less than 95%; and those with more than 95% were defined as cases and controls respectively.

The third study was an observation study which documented experiences and lessons generated in the process of implementing ART services at Chalinze health centre. Clinical procedures were evaluated and document review was carried out to solicit patients' characteristics and enrolment rates.

Main findings

Of the 421 HIV-1 infected patients studied for parasites co-infection, 198 (47%) were co-infected with one or more parasites. While 93/421(22.1%) patients had helminths only co-infection, and 50/421(12.9%) had *Plasmodium sp* only co-infection. The most frequently helminths diagnosed included hookworm 65/421(15.4%), Schistosomiasis 49/421(11.6%), *Strongyloides stercoralis* 57/421(13.5%), and *Ascaris lumbricoides* 54/421(12.8%). There was no statistical associations between CD4+ T-lymphocyte counts <200/µl, or WHO clinical stage III/IV with parasites co-infections (AOR 1.2, 95%CI 0.8-1.8).

Anaemia was common in parasite co-infected patients (32.5% vs. 18.8%). Parasites co-infection was associated with risk of anaemia (AOR 2.1, 95%CI 1.3-3.2). In multivariable logistic regression analysis, baseline CD4+T cells <200/µl was significantly (AOR 2.4, 95%CI 1.3-4.7) associated with CD4+Tcells <200/µl at six months. HIV-1 P24 antigen mean concentration was higher in parasites co-infected patients (ranges 47.6 to 56.9pg/µl) compared to patients without parasites co-infection (5.5pg/µl).

HIV/AIDS clinical presentation showed that weight loss was the commonest symptom (48.3%); followed by chronic cough (40.8%). Most symptoms were found to be highly specific (ranging from 56.4% to 98.6%) with high positive predictive values (ranging from 57.9% to 80%) in predicting severe immunosuppression using CD4d”350 as ‘Gold standard’. Chronic diarrhoea presented in 10.6% of patients, and predicted well severe immunosuppression alone or in combination of symptoms (with high likelihood ratios ranging from 1.83 to 3.27 at 95%CI). Headache, skin and fungal diseases presented highly but relatively weak in predicting immunosuppression.

The combination of 3 symptoms correlated with the WHO stages III/IV with high specificity and positive predictive values, but had

lower sensitivity. The sensitivity of all the presenting symptoms remained lower than 52%, and was not improved by including more signs and symptoms in the analysis.

In the evaluation of factors related to non adherence to ART, a total of 79 cases (non adherence) and 237 controls (adherent) matched by age and sex were studied. A high proportion of cases and controls (77.2% and 84.8%) had good knowledge of ART benefits, adherence and eligibility. Majority of cases (73.3%) and controls (69.2%) used public transport to access ART services. In the univariate analysis: missed clinic appointments due to lack of fare or other reasons and was associated with ART non adherence (mOR 4.2, 95%CI, 2.2-8.1 and 2.1, 95%CI 1.2-4.2, respectively). Disclosure to confidants only and failure to disclose HIV-test positive status were associated with non adherence (mOR 3.3, 95%CI 1.3-8.5 and 2.3, 95%CI 1.2-7.1, respectively). Alcohol use was associated (mOR 1.9, 95%CI 1.4-3.7) with non adherence to ART. Patients who were not satisfied with providers were more likely to be non adherence to ART (mOR 2.0, 95%CI 1.2-3.8). In the multivariate analysis same factors were found to be associated with no adherence to ART.

The study at Chalinze health centre showed that, 611 care and 284 ART patients were attended between May 2007 and June 2009. Majority of patients 762/895 (85.1%) were adults aged 25-45 years, while children were 27/611 (4.4%) pre ART and 16/284 (5.6%) ART. In total 550/895 (61.5%) patients had CD4+T lymphocytes d”350/µl the cut-off point for initiating ART. The frequency of symptoms was noted to significantly decrease with increasing CD4 counts (p<0.001).

In conclusion, we have looked at one set of parasites and found high prevalence of malaria and helminths co-infection in HIV-infected individuals. Based on local helminths epidemiology and HIV-infected cohort specific helminths co-infection prevalence data, mass treatment of soil transmitted helminths can be

confidently incorporated in HIV/AIDS care and treatment programs.

HIV/AIDS clinics managing large cohorts should review and validate site specific HIV clinical manifestations in comparison with CD4 counts and WHO clinical stages. Based on local experiences simplified guidelines are useful for resource constrained settings without CD4 counting facilities.

These findings show that adherence is a dynamic process that varies depending on region or cohort specific adherence factors. Adherence improvement strategies need to consider site specific adherence determinants, patient experiences and concerns.

ART services can successively be provided at health centre level and encourages HIV-infected persons to seek care. However, clinicians need regular clinical mentorship and supportive supervision.

Part I

Introduction

Chapter 1: Emergence and Evolution of HIV and AIDS

1.1 Global Burden of HIV/AIDS

In 2009, UNAIDS and WHO published data showing that there are 33.4 million people living with HIV/AIDS globally. Sub-Saharan Africa is the most affected region with 22.4 million people living with HIV/AIDS. During the same period 2.7 million people became infected with the human immunodeficiency virus (HIV), 1.9 million from sub-Saharan Africa and 2.0 million deaths were accounted for by AIDS worldwide while 1.4 million deaths occurred in sub-Saharan Africa. The prevalence of HIV varies considerably across sub-Saharan Africa ranging from less than 1% in Niger to over 25% in Swaziland. About two thirds of infection is through men to women sex (1) (2). Women account for approximately 60% of people living with HIV/AIDS (1).

1.2 History and epidemiology of HIV

The origin of the global HIV-pandemic is difficult to determine and when and where the first cases of AIDS and or HIV infection occurred are still unknown. However, retrospective studies in central Africa reported on the epidemic increases of clinical diseases markers of AIDS in the late 1970's and early 1980's. In addition, HIV was later identified in blood samples collected from central Africa which pointed to the earlier occurrence of HIV infection in central African countries.

The first reported AIDS cases were defined in young homosexual men in United States of America in 1981, who presented with aggressive Kaposi's sarcoma and *Pneumocystis carinii* pneumonia (3)(4)(5). During the same period, new cases of fatal wasting disease were described in sub-Saharan Africa in heterosexual men and women (6). Subsequently epidemiologic and virologic investigations identified the cause of AIDS as Human Immunodeficiency Virus (HIV) (7)(8).

The route of HIV transmission was described few years later following observational studies in Europe, sub-Saharan Africa and America (9)[(10)(11). Although the disease affected different groups of the population in each of the three continents, it become apparent that HIV was transmitted through heterosexual and homosexual contact; infected blood transfusion; intravenous drug use by sharing needles, therapeutic practices and vertical transmission from mother to child (MTCT)(11)(10)(12). In sub-Saharan Africa, HIV transmission is largely through heterosexual contact in adults, but also through MTCT and therapeutic practices.

During the early years of the epidemic it became clear that HIV/ AIDS was already spread worldwide killing young adults (15-49 years). Sub-Saharan Africa was severely affected, harbouring two thirds of the global total numbers of HIV (13). Within the first decade of the pandemic, sub-Saharan Africa experienced a generalized epidemic and was hit hard by the disease. Many countries of the region reached HIV prevalence of 10% to 40% (14).

Socio-cultural, civil unrest in the great lakes and economic factors facilitated the quick spread of HIV in sub-Saharan Africa region (15). Wide spread poverty, and cultural practices that encouraged inheritance of widows and ritual cleansing played a substantial role in HIV transmission (16) (17). Poverty forces young women to engage into commercial sex; while young men migrate to urban centres as traders and casual manual workers. These economic activities exposed both young men and women to high risk sex behaviour. The presence of behavioural factors and the biologic influence of Sexually Transmitted Diseases (STD) facilitated rapid transmission of HIV (18).

1.3 Global HIV prevention methods

After recognition of the major routes of HIV-infection, prevention measures were designed and instituted globally. HIVIAIDS awareness creation through mass education campaigns using public media; and declaration of one's HIV-positive status in public; especially that of celebrities, created awareness of the disease and helped to draw attention of the international community (19). **A**bstinence; **be** faithful to one partner; and use of **C**ondom (ABC) were introduced and still are key measures to curtail further spread of the disease (20). Male and female condoms provide a proven and affordable prevention option (21). Other measures include prevention of mother to child HIV transmission (PMTCT) by use of Nevirapine, AZT or combination therapy (22). Blood screening for HIV and Syphilis before transfusion; and voluntary counselling and testing (VCT) are important interventions undertaken to prevent HIV infection. Needle exchange programs were introduced as part of the prevention methods for Intravenous Drug Use (IDU) (23).

Recently, additional prevention measures include male circumcision, vaginal microbicides and use of antiretroviral in post-exposure prophylaxis (24) (25). Male circumcision has been endorsed by the World Health Organization as one of the preventive measures after results of multi-country clinical trials conducted in Kenya, Uganda and South Africa (26). Vaginal microbicides the only prevention method that can be controlled by women have been waited for more than two decades. Recently, a South Africa clinical trial produced results on vaginal microbicides containing tenofovir gel which provided efficacious protection against HIV-1 transmission in women (27). It is the first time for a biological intervention against HIV-1 to be very successful with high level of efficacy. HIV-1 vaccines as prevention methods are under development (28), and several candidates are at various stages of development (29). The existence of different HIV-1 sub-types and the continuous

mutation of the virus posses a great challenge to development of universal vaccine. In sub-Saharan African region alone there is more than 5 different sub-types genetically distinct HIV-1 isolates (30) (31).

Successful implementation of the fore mentioned measures depends heavily on a country's political will, economical development and readiness to acknowledge HIV as a human disaster and availability of international community support (32). Uganda and Senegal represent two success stories in sub-Saharan Africa. Uganda has brought estimated prevalence rate down to 5% by the end of 2001 from an estimated peak of close to 14% in the early 1990s with strong prevention campaigns (20). HIV prevalence has stabilized in Senegal at a relatively low level (30). Uganda responded much earlier to the epidemic than Tanzania. Tanzania government acknowledged HIV/AIDS as a human catastrophe in 1999 almost two decades after the first case was described in Kagera Region (33).

1.4 HIV and AIDS care and treatment

In 1986, dramatic progress in the medical treatment of AIDS was made by the introduction of azidothymidine or Zidovudine (AZT), an anticancer drug that was effective at slowing down the HIV virus (34). The U.S Food and Drug Administration approved the use of dideoxycytidine (ddC) in combination with AZT for adult patients with advanced HIV infection who were continuing to show signs of clinical or immunological deterioration. This was the first successful use of combination drug therapy for the treatment of AIDS. More drugs were gradually introduced into medical practice, including Lamivudine (3TC), Nevirapine and others (35) .

Successive use of combination antiretroviral therapy and the improvement in health of those had been ill in hospitals in the USA, created hopes of a complete cure. The approach to

treatment was described as “hit early, hit hard”, starting ART with the goal of virologic suppression and eliminate all reservoirs. It was learnt that aggressive treatment with multiple drugs can convert deadly AIDS into chronic, manageable disorder like diabetes. Important issues of drug toxicity, resistance and adherence became considerations (36).

Currently, there are more than 19 antiretroviral drugs approved for the treatment of HIV infection, in 3 mechanistic classes (37) (31): HIV reverse transcriptase inhibitors, HIV protease inhibitors and HIV entry inhibitors. Nucleoside Reverse Transcriptase Inhibitors (NRTIs): the primary mechanism of action of this class is inhibition of viral RNA-dependent DNA polymerase (reverse transcriptase) enzyme. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) unlike the NRTIs, they are not directly incorporated into the viral DNA but instead inhibit replication directly by bind-ing to the enzyme reverse transcriptase. Resistance to these drugs develops rapidly, especial-ly when used alone. Protease Inhibitors (PIs) competitively inhibit the HIV protease enzyme whose activity is critical for the terminal maturation of infectious virions (37) (31). This inhibition prevents the maturation of virions capable of infecting other cells. HIV entry inhibitors include CCR5 inhibitors and integrase strand transfer inhibitor (37).

1.4.1 HIV and AIDS current case management

Until 2004, because of high cost and complexity of administering ARVs, drugs were mostly limited to treating HIV-infected patients in the developed world (38). Due to global initiatives the prices of antiretroviral drugs have fallen sharply, treatment is becoming widely available and is provided free in developing countries. HIV case management is different between developed and developing countries due to variable resources availability. Patient assessment, monitoring and treatment in developed countries involve a range of complex laboratory testing and many drug

regimes as compared to developing countries. For example in USA, drug resistance testing before initiation of therapy and use of CCR5 inhibitors (Maraviroc) which are expensive undertaking in developing countries. WHO developed guidelines for ART to be used in resource limited countries and is adapted to country specific conditions (39). But still there is variability in HIV case management in resource limited countries between central and peripheral (rural) clinics due to uneven resources allocation which tend to favour the central clinics.

1.4.2 Patients' entry to HIV and AIDS care and treatment

Patients are identified after a HIV-positive antibody test from: voluntary counselling and testing units (VCT); PMTCT at RCH services and Provider Initiated Testing and Counselling (PITC) in medical wards and outpatient clinics; tuberculosis clinic; sexually transmitted Infection (STI) clinic. HIV-1 infection can be diagnosed by detection of specific antigens (DNA PCR in infants and children<2years), antibodies or both from plasma, whole blood, serum, or saliva. Health care workers provide rapid HIV tests (A sequence of two tests) and confirmatory tests may be performed by using ELISA test or Western blot (where available) in laboratory (40). Before the test is performed; the patient is taken through a session of counselling and HIV education in a group or one by one counselling depending on the setting [(41). Then, the patient has the option of accepting the test (Opt-out). After confirmation of the HIV-positive status the patient is referred to the Care and treatment clinic for continuous management and monitoring.

1.4.3 Initiation of antiretroviral therapy

The initial assessment of a HIV patient includes clinical and laboratory evaluation (42). Then, the patient clinical disease is classified according to WHO clinical disease staging criteria (43): Stage 1- Asymptomatic; Stage 2-Mild disease; Stage 3-Advanced disease; and Stage 4-Severe disease. In places where laboratory

investigation are not available; Patients with WHO clinical stage 3 or 4 are eligible for starting ARVs treatment.

Laboratory investigation such as haematology, chemistry and CD4 cell counts are done to provide addition information and treatment monitoring. ARV treatment is better commenced after a combination of clinical and immunological staging. Although there are addition considerations but a patient with CD4d”350 cells/mm3 is eligible to start ART regardless of clinical stage. Previous guidelines considered the cut-off point of CD4d”200 cells/mm3 as a threshold at which the body can still mount immune response and below which the risk of Opportunistic Infection increases. Patients with HIV and tuberculosis co-infection regardless of CD4 cell count levels and pregnant women with CD4d” 350 cells/mm3 are eligible for ART. ART is not indicated for patients with CD4>350cells/mm3. Beyond clinical eligibility, it is important that the patient’s willingness, readiness and ability to be on ART adherently be assessed and addressed. The patient is made to understand that ART is a lifelong treatment; and the importance of adherence to treatment and common drug toxicities (39).

The best time point to start ART treatment to asymptomatic patients with CD4>350cells/mm3; and modest levels of viraemia (less than 100,000 copies per ml); remains controversial (40) (36). Early depletion of gut CD4 lymphocytes, increasing viral diversity and the poor generation abilities of key populations of the immune system provide arguments for beginning treatment as early as possible. Additional considerations include long-term drug toxicities; treatment costs and immune reconstitution disease are some of the complications of long term HAART (41).

Cotrimoxazole prophylaxis is recommended to all HIV infected patients with CD4<350 cells/mm3 or clinical stages 2, 3 and 4 including pregnant women in resource limited settings. Clinical trials have showed consistent benefit of *Cotrimoxazole*

prophylaxis in the reduction of morbidity and mortality among people living with HIV with varying CD4 counts with and without Mycobacterium tuberculosis (44).

The recommended criteria to start ART confer benefit to patients on continuous clinical monitoring identified prior to profound immunosuppression. Studies have shown that patients presenting with pre ART of CD4<50cells/mm3, have a greater risk of death soon after starting ART (45). Several factors may account to this high risk of mortality: at a lower CD4 cell count severe opportunistic infection occurs including disseminated Tuberculosis (46); Immune reconstitution inflammatory syndrome tend to occur more frequent in patients with lowest CD4 cells. Patients in resource limited settings usually are identified late in the disease progression with CD4<200cells/mm3 or clinical stage 4. ART-LINC collaboration recoded 4% mortality rate in the first six months which dropped to 2% in the next 6 months of active patients follow up. The early deaths were attributed to advanced disease (47).

1.4.4 Antiretroviral therapy

The standard of care for treatment of HIV infection has evolved from the use of single-drug therapy, to dual-nucleoside analogue therapy to the current standard of care, 3-drug therapy with 2 nucleoside analogues in combination with a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor. First line ARV combination regimen for adults and adolescent ART naive patients recommended by the WHO for use in resource limited settings includes (39):

I. Stavudine (d4T) +Lamivudine (3TC) or Emtricitabine (FTC) +Nevirapine (NVP
II. Zidovudine (AZT) +Lamivudine (3TC) or Emtricitabine (FTC) +Nevirapine (NVP)
III. Stavudine (d4T) +Lamivudine (3TC) or Emtricitabine (FTC)+Efavirenz (EFV)
IV. Zidovudine (AZT) +Lamivudine (3TC) or Emtricitabine (FTC)

+ Efavirenz (EFV)

V. Tenofovir (TDF) +Lamivudine (3TC) or Emtricitabine (FTC) + Efavirenz (EFV) or Nevirapine (NVP

Second line ARV combinations include:

I. Tenofovir (TDF) +Lamivudine (3TC) or Emtricitabine (FTC) + atazanavir (ATV) with boost ritonavir or lopinavir/ritonavir

II. Zidovudine (AZT) +Lamivudine (3TC) +atazanavir (ATV) with boost ritonavir or lopinavir/ritonavir

These combinations were formulated considering less drug toxicity, simplification of administration, less antagonism and few chances of early development of viral mutations (41). Common early and potentially severe toxicities are hypersensitivity to NNRTIs (EFV and NVP) occurring within the few weeks of therapy (48). Others include AZT-related anaemia and neutropenia presenting within few months after initiation of therapy (49). Stavudine causes long-term toxicities e.g. lipoatrophy and peripheral neuropathy; Stavudine is no longer in use in USA and Europe and is been phased out in resource limited settings (42). It is still in use in developing countries for reasons of cost and availability. Hepatic, renal and lactic acidosis drug toxicities require laboratory tests to be identified. Common ARV toxicities can be summarized in the following groups: Haematological toxicity most seen with AZT(50); Mitochondrial dysfunction seen with NRTI drugs; Renal toxicity seen with IDV and TDF; Allergic reactions caused by NNRTI and sometimes NRTI, ABC and some PIs; other metabolic abnormalities are more common with Protease Inhibitors (51) .

1.4.5 Clinical and laboratory monitoring of patients on ART

Ideal patient and ARVs drugs monitoring involve: clinical progression; immunological; viral load measurement; and drug resistance monitoring. Drug resistance monitoring testing (by use of both genotyping and phenotyping); viral load (HIV RNA levels) measurement; and CD4 T-lymphocytes cell count in adults and

CD4% in infants are part of the routine standard care in developed countries(39).

In most sub Saharan countries patient monitoring is limited to: Clinical progression based on WHO disease stages and limited laboratory tests. Laboratory tests performed include haematological, biochemistry and CD4+ T-lymphocyte counts. Each patient should have at least these tests done at baseline before initiating treatment. CD4+ T-lymphocyte count can then be repeated at least every 6 months. Monthly assessment of haematological and biochemistry parameters are performed to assess drug toxicities. ELISA assay of HIV-1 P^{24} antigen in plasma is another method that can be used to monitor patients on ART in places where viral load is not available (52). P24 ELISA assay is relative less expensive compared to viral load measurements, thus can be adopted for use in rural district hospitals.

However, these methods and parameters cannot be used to monitor patients in peripheral (rural) health centres due to lack of qualified staff and laboratory equipments. Only district and referral hospitals can perform these tests. Again, routine daily shipping of samples from rural health centres to district laboratories is challenged by logistic issues like transport problems and costs. It is therefore important to research the minimum essential laboratory requirements that can be used to monitor HIV patients in rural settings.

Good clinical progression is assessed by determination of weight gain and reduced morbidity from opportunistic infections; and improvement in patient's quality of life. Appearance or persisting opportunistic infections, or lack of weight gain, may indicate treatment failure and so the need to consider changing regimens. Treatment is to be considered successful if the viral load decreases by 1 to 2 logs (10 to 100 folds) from the baseline level. However in most cases, CD4+ T-lymphocyte count will be used instead of viral load thus a rise in CD4+ T-lymphocyte count

will indicate success. Treatment failure on the other hand is indicated by a viral load increase of 0.3 to 0.5 logs or a 30% fall in CD4+ T-lymphocyte count (39).

1.4.6 Treatment failure

The introduction of HAART worldwide improved the trends of HIV/AIDS morbidity and mortality even in developing countries (53). Patients can now survive longer than before HAART (54) (55). Great efforts of the international community have been employed to assist developing countries, especially sub Saharan Africa to fight AIDS. The combined efforts resulted in better understanding of the dynamics of the epidemic. Universal access to care and treatment through the UNAIDS “3by5” agenda is achieving success in making ARVs available to the poor communities in countries like Tanzania (43).

However, treatment failure causes a considerable challenge to both patients and providers. Currently, there is no standard definition of treatment failure. The WHO defines treatment failure in three groups of clinical failure, immunological failure (based on CD4 cell count) and virological failure. Clinical failure is considered when there is new or recurrent WHO stage 4 conditions (with exemptions) (39). Immunological failure is defined as fall of CD4 cell count to pre-therapy baseline (or below); or 50% fall from the on-treatment peak value; or persistent CD4 levels below 100cells/mm3. Virological failure is considered when plasma viral load is greater than 10^3 copies/ml. Several other clinical and immunological issues need to be considered before deciding existence of treatment failure. While virological failure is inability to achieve an undetectable HIV-RNA (<50copies/ml) after six months of HAART or sustained rise of HIV-RNA of >50copies/ml or >400 copies/ml following suppression below this level (56).

There are a number of causes of treatment failure which include: HIV virus mutation; baseline patient characteristics; baseline drug

resistance; suboptimal adherence (57); drug side effects and toxicity; pharmacokinetic issues; and other reasons specific to individual patients. In the Swiss and Hopkins HIV Cohort Studies, some of the factors which were associated with higher risk for virologic failure included lower CD4 cell count and symptomatic HIV disease at presentation prior to ART and missed clinic appointments (58). In addition suboptimal adherence to ART is associated with treatment failure. These reasons are common in rural limited resource settings in Tanzania (59).

1.4.7 Access, Availability and Adherence to ART

Access to ART is a major challenge in sub-Saharan Africa due to limited resources and the high burden of HIV and AIDS. At the end of 2008, the estimated coverage of ART in this region was 44% (60). Despite this encouraging progress, the majority of patients in need of ART in peripheral (rural) areas still are unable to access treatment given the distances from ART clinics. The few patients that access ART cannot sustain regular monthly follow-ups and often drop out of treatment. In recent years, considerable energy and money have been spent trying to achieve universal access to treatment for HIV and AIDS. Such efforts have generated replicable experiences regarding provision of ART in peripheral (rural) settings. The extraordinary chronic disease clinic at Saint Francis Designated District Hospital at Ifakara is one of the few peripheral based programs reaching the poor patients in need of ART (61). This program highlights major issues in the process of scaling-up ART in resource limited peripheral settings: first is the need for a functional patient referral system; secondly uninterrupted supply of ART. Stock out of ART is critical in these remote (peripheral) areas where patients cannot afford return multiple clinic visits. The third lesson learned is the use of treatment assistants, who support the patient to access and adhere to ART.

Non adherence to therapy is a major cause of drug resistance. It might be inevitable after prolonged periods of ARV use to develop

resistance. However, the major interest is to delay drug resistance development because there are limited available drug regimens options. A patient is expected to achieve more than 95% of adherence to protect resistance viral strain development (62). This level of adherence is challenging in resource constrained settings. Social and economic factors impact on the patients' capacity to achieve adequate adherence (63). Provision of free antiretroviral therapy and promotion of social coping may enhance adherence and reduce possibility of development of drug resistance (59). Stigma, poverty and distance from the care and treatment centres are some of the socio-economic barriers to adequate adherence to therapy. Other factors found to be associated with drug resistance development include lower CD4 cell of <200 cells/µl, and the missing of a scheduled clinic visit in the past month (64). These factors are frequently found in resource limited countries. Population socio-economic diversities, antiviral drug resistance and the HIV virus dynamics need to be closely studied.

Pill burden and drug toxicities are additional problems contributing to poor adherence to ART (65) (66). Pill burden is been addressed by development of fixed dose combination formulations; and drugs with long half life which can be taken once a day. A strategy to ensure lifelong compliance to HAART was suggested to be structured treatment interruptions. The rationale for this approach was based on the theory that the body immune system can control low levels of viral replication after suppression by HAART. Treatment interruption was proved to have no clinical benefit in the SMART trial (67).

Several approaches are used by health care providers at care and treatment clinic to monitor patient adherence to ARVs and prophylaxis of opportunistic infections (OI). The most commonly used are pill count; pharmacy records; patient adherence to scheduled visits and clinicians assessment. These methods are useful monitoring tools when applied in combination.

Chapter 2: Co-morbidity, Opportunistic Infection and Interaction

Residents of sub-Saharan Africa experience more ill health than people in other continents. This is due to the presence of endemic infectious diseases coupled with HIV-infection and Opportunistic infections.

Co-morbidity can be defined as occurrence of combination of disease conditions in the same person at the same time. Opportunistic infections include all infections and malignancies which occur when the immune system is weakened. There are different diseases causative agents found in the tropics, including viruses, bacteria, fungi, protozoa, helminths and arthropods (68). A relatively small percentage of these pathogens cause a majority of serious health effects to HIV-infected persons (69). The distribution of these pathogens is very diverse depending on favourable environment, social behaviours and ecological factors that result in their transmission (70).

HIV and tropical infections affect each other mutually (71). HIV infection may alter the natural history of tropical infectious diseases, impede rapid diagnosis, or reduce the efficacy of ant parasitic treatment (72). Tropical infections may facilitate the transmission of HIV and accelerate progression from asymptomatic HIV infection to AIDS. Disease severity depends on the virulence of the infecting organisms and the competence of the immune system of the infected person (73). People with weakened immune system experience much more severe disease even to causes of mild infections (74). Persons infected with sexually transmitted diseases especially those associated with genital ulceration, have increased susceptibility to HIV-infection due to lack of skin protective barrier.

Activation of the immune system by tropical infections renders the T-cell lymphocytes susceptible to HIV infection which results

into HIV disease progression (75). Infections that activate the immune system and increases secretions of cytokines, chemokines and chemokines receptors have been shown to increase the susceptibility and pathogenesis to HIV-virus infection (76). Diseases like mycobacterium tuberculosis and soil transmitted helminths which causes up-regulation of CCR5 expression facilitates HIV infection in individuals with these infections (77). Infections that affect the cellular immune system have been shown to increase HIV-1 virus replication which results in disease progression (73).

On the other hand, effects of HIV-infections on tropical diseases are the result of compromised cellular immune system because HIV targets $CD4^+$ T lymphocytes and macrophages (37). Thus, organisms that require intact cellular immune system for their eradication can easily cause infection (78). The compromised immune system increases susceptibility to new infection and reactivation of latent infection (73). As result, HIV immunosuppression facilitates infections, increase the rate of infection, change disease presentation and may complicate treatment. Most of the major tropical diseases depend on CD4 T-cell lymphocytes and macrophages for their elimination from the body, thus HIV infection fuels parasitic diseases (79). For example, risk of parasitaemia and clinical malaria is increased in semi immune HIV infected adults in malaria regions (80). Isospora belli and cryptosporidium results into severe chronic diarrhoea disease in HIV infected persons.

These observations may explain why HIV in sub Saharan Africa is easily transmitted, and has a faster clinical progression and high mortality. Again, the above citations can explain the variations in clinical presentation of HIV in this region. At the beginning of the epidemic, chronic diarrhoea, wasting (slim disease), chronic fever without an obvious source, and pulmonary disease were the syndromes that marked AIDS (68). The clinical picture of AIDS had changed; the clinical presentation depends

on the prevalent infectious agents. In holoendemic malaria regions recurrent malaria fever episodes is most common in HIV infected persons (80). Enteropathic AIDS is most common in some areas, usually accompanied with diarrhoea (81). Tuberculosis, both pulmonary and extra-pulmonary, is the supreme complicating infection. Herpes zoster is frequently the first clinical presentation, and has a 95% positive predictive value for HIV positive status (82). While in other settings septicaemia due to non-typhoid salmonellae, Escherichia coli and Streptococcus pneumoniae was the most common diagnosis in HIV-infected persons (73)

The current understanding of the interaction between HIV and tropical diseases calls for further research on; patient response to treatment in presence of co-infection. And, further elucidation of the manifestation of HIV-related diseases in peripheral (rural) settings is needed to optimize patient clinical care.

The importance of opportunistic infection to human health was manifested by the emergence of HIV. The risk of different groups of opportunistic infections typically increases at different stages of HIV infection in relation to CD4 T-cell lymphocytes count depletion. At CD4 T-cell lymphocytes count of 200-400 patients may develop herpes zoster, tuberculosis and oral Candidiasis. While at CD4 T-cell lymphocytes count of lower than 200 cells/µl, several other diseases appear, including *Pneumocystis carinii* pneumonia, *Mycobacterium Avium* complex and others (44). The highest risk for Opportunistic Infection occurs when the CD4 count is between 50-100 cells/µl. Some of these diseases can infect people with normal immune systems, but with HIV, they occur at a much higher rate. It also takes longer for a person with HIV to recover from a disease than it takes for someone with a healthy immune system.

Table 2. 1: Distribution of selected opportunistic infections reported from studies in sub-Saharan Africa*

COUNTRY	Summary of common Opportunistic Infections
Central Africa	Cryptosporidium species, Salmonella species
Uganda	Cryptococcus neoformans, Candida albicans, Cryptosporidium species, Salmonella species Streptococcus pneumoniae, Mycobacterium tuberculosis, varicella zoster virus
Ethiopia	Cryptosporidium species, Salmonella species, Mycobacterium tuberculosis
Kenya	Cytomegalovirus, Cryptosporidium species, Salmonella species, Streptococcus pneumoniae, Mycobacterium tuberculosis, Pneumocystis carinii pneumonia, Mycobacterium Avium complex, Toxoplasmosis
Rwanda	Cryptococcus neoformans, Mycobacterium tuberculosis, Malaria Pneumocystis carinii pneumonia, varicella zoster virus
Burundi	Cytomegalovirus, Mycobacterium tuberculosis, Pneumocystis carinii pneumonia, varicella zoster virus
Tanzania	Cryptosporidium species, Mycobacterium Avium complex, Pneumocystis carinii pneumonia, Streptococcus pneumoniae Salmonella species, Toxoplasmosis, Mycobacterium tuberculosis
Malawi	Cryptococcus neoformans, Cytomegalovirus, Malaria, Mycobacterium Avium complex, Mycobacterium tuberculosis Pneumocystis carinii pneumonia, Salmonella species, Streptococcus pneumoniae
Zimbabwe	Varicella zoster virus, Pneumocystis carinii pneumonia, Cryptococcus neoformans, Cryptosporidium species
South Africa	Pneumocystis carinii pneumonia, Salmonella species, Streptococcus pneumoniae, Mycobacterium tuberculosis, Cryptococcus neoformans, varicella zoster virus, Candida albicans, Cytomegalovirus, Mycobacterium Avium complex,
Botswana	Varicella zoster virus
Zambia	Pneumocystis carinii pneumonia, Mycobacterium Avium complex, Mycobacterium tuberculosis, Cryptosporidium species
Congo	Pneumocystis carinii pneumonia, Malaria, Mycobacterium tuberculosis
Cameroon	Streptococcus pneumoniae
Ghana	Cryptococcus neoformans, Candida albicans
Ivory cost	Pneumocystis carinii pneumonia, Salmonella species, Streptococcus pneumoniae, Toxoplasmosis, Cytomegalovirus, Mycobacterium Avium complex, Mycobacterium tuberculosis, Cryptococcus neoformans, Cryptosporidium species
Gambia	Cytomegalovirus
Senegal	Toxoplasmosis

* Adaptation from Charles B Holmes et al Review of Human Immunodeficiency Virus Type 1-Related Opportunistic Infections in Sub Saharan Africa: HIV and AIDS 2003

When the immune system is very weak due to advanced HIV disease or AIDS, some infections can result into systemic dissemination (Visceral leishmania) (83). Diseases like AIDS that spread to involve a number of different organs, posses a great challenge to clinical management. Similarly, opportunistic infections appearing at a late stage of HIV infection usually result in a poor prognosis. For instance, Cryptococcus meningitis can occur with a CD4 T-cell lymphocyte count < 100 cells/µl and is associated with high mortality (84).

Mycobacterial tuberculosis is one of the most common opportunistic diseases that carry the highest cause of morbidity and mortality in HIV infected patients. HIV and Mycobacterium tuberculosis have a synergistic interaction; each accentuates progression of the other resulting in increased morbidity and mortality in poor settings (86). Atypical mycobacterial also cause serious disease in immunocompromized patients (86) (87). Mycobacterium Avium complex is reported to complicate Immune reconstitution Syndrome in the first 3 months of ART initiation (88). Its diagnosis requires culture of lymph node fine needle aspirates. Therefore, it is difficult to diagnose Mycobacterium Avium complex in areas with limited access to laboratory with capacity to perform mycobacterium culture.

Various types of fungal infections are also common among HIV-infected patients. However, Cryptococcus neoformans and *Pneumocystis carinii* Pneumonia are the most common life threatening fungal infection in AIDS patients (89)]. Candidiasis, despite of being the commonest fungal infection in HIV/AIDS patients, its overall impact in patient disease progression and outcome is less documented in sub Saharan Africa. A study in Uganda found Oral Candidiasis in more than 70% of TASO clients and was reported to cause mild to moderate discomfort to the patients (90). However, the study did not describe the clinical and immunological impact (CD4 increase) of Candidiasis to the patients after treatment.

Diagnosis of Opportunistic Infection is variable, some can be diagnosed clinically and others require laboratory tests for confirmation. Opportunistic Infection with unique skin lesions like Candidiasis and Kaposi's sarcoma can be diagnosed clinically with certain. While other Opportunistic Infection which present with multiple signs and symptoms like Tuberculosis, Pneumocystis Carinii Pneumonia and Cryptococcus may require combination of both clinical and laboratory tests to make a diagnosis. Other diagnosis methods for Opportunistic Infection include: Microscopic examination, biopsy, X-ray, Blood tests and other disease specific specialized methods.

Most of the Opportunistic Infections are preventable; either by use of ART or specific drugs recommended for prophylaxis of Opportunistic Infection. For example, use of co-trimoxazole can protect patients from Pneumocystis Carinii Pneumonia, Toxoplasmosis gondii and some other enteric protozoa. Fluconazole and Azithromycin protects against Cryptococcus and M. Avium respectively (91). The main challenge remains to be adherence to therapy and implementation of the guidelines. In addition data is lacking on the actual prevalence of Opportunistic Infection, levels of adherence to therapy and pattern of guidelines implementation in rural settings.

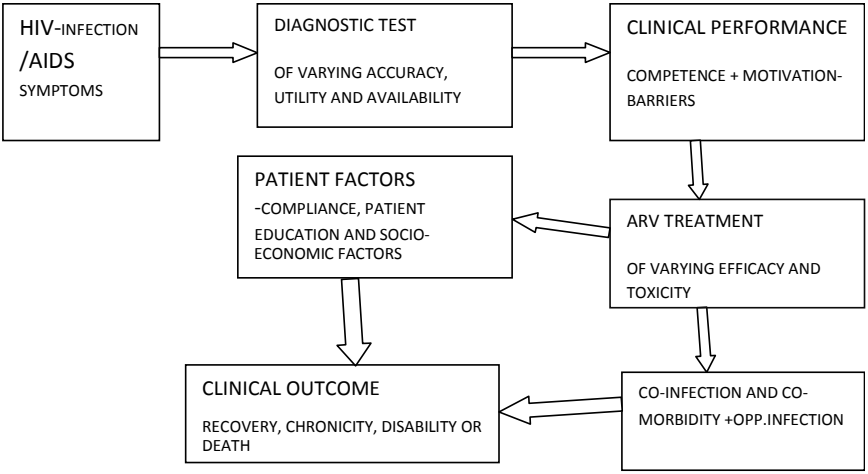

Figure 2. 1: Conceptual Framework

Figure 3.1: Water crisis in the study area

Chapter 3: Epidemiology and Prevention of HIV and AIDS inTanzania

3.1 HIV-1 epidemiology in Tanzania

HIV was initially found in a geographic band stretching from Central Africa across to countries of East and Southern Africa (14). The epidemic began gradually to move south through Uganda, Kenya and Tanzania to Southern African countries. The first cases of AIDS were described in a hospital in Kagera region western Tanzania in 1983. Apparently, AIDS was locally associated with cross border trade between Uganda and western Tanzania. Initially, HIV affected mostly traders and was named "Juliana" because of the popular brand of shirts imported from Uganda at that time. The disease quickly reached all big urban centres of Tanzania. Prostitutes and their clients suffered from profuse chronic diarrhoea and profound loss of weight, and then AIDS was named "Slim disease". The same "Slim" disease was already described in Uganda and Zaire (92)

By 1985, the country had an estimated HIV prevalence of 1.3%, which increased steadily to reach 7% by the end of 2004 (93) (94). In 2003, between 1.2 and 2.3 million people in the age group 0-49 years were estimated to be living with HIV/AIDS. The most vulnerable and affected groups include: women 30–34 years old; and men 40–44 years old; sex workers; people in the transport sector, mines, police force, military, prisons and prisoners; refugees. Occasionally, a few elderly people get HIV-infection while caring their sick relatives and some forced into new roles as caregivers without support themselves (95). Urban residents tend to have higher prevalence as compared to rural residents. However, overall women are much more affected than men, and the prevalence increases with age, education level and wealth quintile (94). Three regions, Mbeya, Iringa and Dar es Salaam, have a particularly high prevalence above 10% (93) (33).

The major route of HIV transmission in the country is through heterosexual contact; exposure to infected blood; mother to child transmission and intravenous drug use. Blood transfusion and unsafe injections might have contributed substantially to HIV infection in children and adults in the early years of the epidemic (96). Needle sterilization by boiling and treatment of severe anaemia due to malaria disease by blood transfusion was common practice while methods of HIV screening of donated blood were not available. Intravenous drug use with needle sharing and re-use is common in big cities, but is more prominent in Zanzibar.

3.2 HIV-1 prevention efforts in Tanzania

Tanzania National AIDS Control Programme (NACP) was established and formally launched in 1988 with the overall aim of coordinating prevention activities, reducing the incidence of HIV infection and its associated morbidity and mortality. A further aim was to establish a link between the government actors and non-government organizations (NGOs) involved in HIV and AIDS activities. This resulted into formulation of HIV and AIDS policies, Tanzania commission for AIDS (TACAIDS) and adaptation and implementation of global preventive measures. NACP receives technical and financial support from Global Fund to fight AIDS, Tuberculosis and Malaria, Clinton Health Initiative and PEPFAR (97). Other organizations like Médecins Sans Frontières are providing additional funds and technical support.

HIV-1 prevention messages and intervention are provided in almost all health care service delivery points in different forms. During routine clinical care patients are informed by health care workers on the importance of abstinence, being faithful to one partner, condom use, early HIV diagnosis and treatment of sexually transmitted infections.

Pregnant women are counselled and tested for HIV-1 at Reproductive and Child Health unit, and those who are found to be HIV-positive receive PMTCT services. While infant feeding counselling and safer pregnancy messages are provided to all antenatal attendees routinely as part of the health education services.

There are also several other prevention programs designed to cover different at risk population groups in all parts of the country. Such as the condom use program which aims at improving access and proper use of condoms, Voluntary counselling and testing, work place HIV prevention for health care workers, male circumcision, and several others. Radio and television broadcast HIV prevention messages.

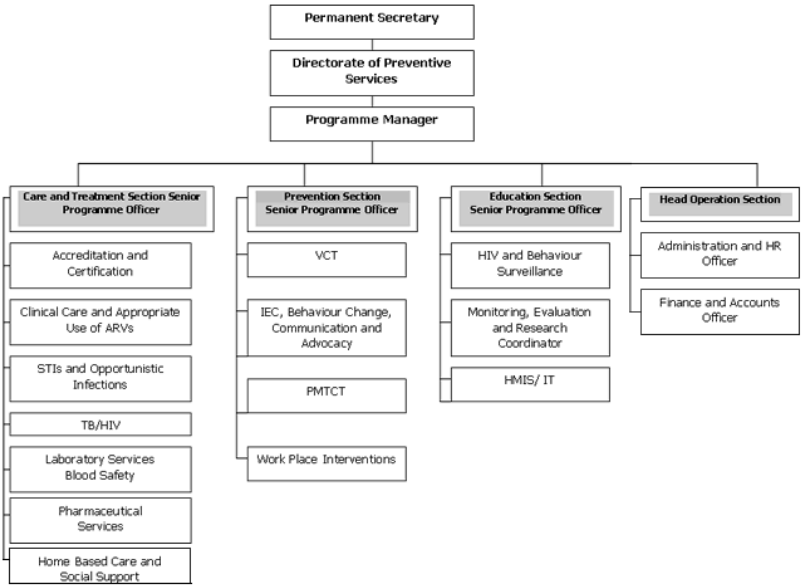

Figure 3. 2: Structure of the Tanzania National AIDS Control Program

3.3 Challenges of expanding Antiretroviral Treatment in Tanzania

The Tanzania National AIDS Control Program provides guidelines and coordinates the provision of free antiretroviral therapy for the whole country. There are major challenges in terms of access and adherence to ART. Despite the achievements of regionalization of non-governmental organizations (NGOs) which have increased ART clinics coverage in the entire country, the majority of patients in peripheral areas travel long distances to ART clinics and cannot be retained into care and treatment due to transport constraints. Although some peripheral ART clinics use treatment supporters to enhance access and adherence to ART (61), such strategies are not yet universal in Tanzania.

These challenges are not limited to Tanzania: the use of ART in sub Saharan Africa (SSA) was delayed for more than a decade after introduction of combination ART in developed countries. The delay was a result of concerns that the weak health systems and adherence problems in SSA populations may lead to widespread ARVs virological resistance (98) (99). Further grounds for concern were related to the possibility of fragmentation of the health system and worsening health care inequalities on the grounds that there were more cost-effective interventions available given the limited funding baskets at the time (100) (101).

There were other numerous health system factors that are still considered to date as major constraints to introducing ART in poor resource settings including inadequate service delivery infrastructure, weak drug regulatory and weak supply systems and demand side barriers (stigma and affordability) (102). It was thought that these barriers would result in poor and unsustained treatment outcomes if not addressed before implementation of ART services.

Health worker shortages in the face of HIV/AIDS have been exposed by the practice of delivering ART through primary health care services. The shortage of qualified staff to be specifically trained and become comfortable in managing medical problems in HIV-infected persons is still a major setback to achieving both a wide coverage and quality of care. In most rural settings, patients are managed by less qualified staff, with poor staff morale caused by logistic difficulties, poor living conditions and lacking appropriate working tools (103). Such factors were considered as serious barriers in scaling up ART and thus initially ART were established in urban hospitals and further delayed in reaching majority of people in rural areas.

There are still more short comings raised against ART scaling-up in resource poor settings which are related to unintended diversion of resources away from other vital health care services such as maternal and child health care services and nutrition (104).

The issue of quality of care and sustainability of services is also considered as a major barrier since sustained funding to ensure an adequate health care system cannot be met by all SSA countries. This is evidenced by failure of African Governments to fulfilling the Abuja declaration to commit 15% of their budgets to health (105). Large-scale access to HIV/AIDS care and treatment and prevention programs in SSA countries have been made possible by donor funded multinational investments. In addition, since ART programs reduce or delay mortality among HIV-infected persons, countries will need to contain an ever-larger numbers of people living with HIV (106). Therefore financial, health system infrastructure and human resources capacity need to be strengthened to cope with the ever increasing demand.

However, these challenges were outweighed by the positive benefits of which the Global initiatives explicitly set out to achieve

in order to save lives of HIV/AIDS patients. In SSA millions of dollars have being directed towards the reduction of medicine prices, infrastructure improvement, hiring and training of staff. The World Health Organization catalyzed these efforts by announcing its aim to help put 3 million people on ART in developing countries by the end of 2005. In Tanzania, a rehabilitation program was initiated where laboratories and consultation rooms were upgraded and provided with all essential equipment. Capacity building programs were undertaken to train of health care workers to enable them to perform HIV-testing, CD4+T lymphocyte counting and HIV/AIDS case management in all hospitals and selected health centres.

Service delivery challenges related to the complex management of ART are being addressed through the use of simple fixed dose ARVs combination regimens, clinical and laboratory monitoring, access to second line regimens and management of side-effects.

3.4 Rationale for the PhD research

The pattern and clinical manifestation of HIV and AIDS is changing continuously due to viral mutations, availability of OIs drugs and co-infections; and is different from place to place. The region and population differences in the clinical picture since the early days of the epidemic were influenced by the endemic pathogens of the affected population and HIV virus mutations (107). With the introduction of ART and OIs prophylaxis, the clinical picture has changed even further. Since HIV/AIDS care and treatment in resource poor settings entirely depends on WHO clinical staging, it is justified to always update our knowledge of HIV/AIDS clinical presentation. The priority is ascertainment of the heterogeneity of the clinical picture in HIV-infected semi-urban and peripheral (rural) populations in order to improve on patient care.

There is a global focus on the management of AIDS and related OIs with little emphasis on co-infectious diseases which are prevalent in resource limited rural areas. This can be explained by lack of clinical data on actual prevalence rate and impact of co-infectious diseases on the health of HIV-infected people. To be effective in providing HIV/AIDS care and treatment in peripheral (rural) settings the emphasis should be proper treatment and monitoring of co-infections and or co-morbidity and treatment of opportunistic infections. Therefore, it is important to estimate the prevalence of co-infections and HIV clinical manifestations in HIV and AIDS patients. This subsequently will result into regular revision of the current HIV and AIDS care and treatment guidelines.

Patient adherence to ART plays a major role in the effectiveness of anti-HIV drugs. Poor adherence to treatment results in ineffective suppression of viral replication which leads to the emergence of drug resistance viral mutations. Adherence to therapy can be monitored and managed at a health facility level by clinicians. Proper monitoring requires understanding of individual patients' living context, barriers and influencing factors to adequate adherence. The current adherence methods in use were developed without consideration of population heterogeneity between urban and peripheral (rural) areas. These differences need to be assessed and find out whether they impact on adherence.

This PhD thesis addressed the above raised questions through a comprehensive approach to crucial issues important for the scaling-up care and treatment services to peripheral (rural) areas.

Figure 4.1: A nurse assistant explaining the study to patients

Part II

Research Goal, Objectives and Principal Methods

Chapter 4 : Goals and Objectives

4.1 The goal of this study

To conduct research to investigate effects of concurrent parasites infections and challenges of HIV/AIDS case management on rural and semi-urban patients in order to contribute information towards better care for HIV/AIDS patients in Tanzania.

Objective 1

To investigate challenges of HIV/AIDS case management related to changing HIV-clinical manifestations and parasite co-infection in rural and semi-urban settings and propose measures to improve HIV-infected patients care.

Specific objectives

1. To determine the prevalence of parasitic co-infections in HIV-infected patients in rural and semi-urban settings of Tanzania
2. To study parasitic co-infections in HIV and AIDS patients and their association with CD4 changes and WHO clinical staging
3. To describe the clinical manifestations of HIV in patients residing in rural and semi-urban settings of Tanzania
4. To develop validated and simplified HIV/AIDS clinical staging based on data generated locally in comparison to WHO clinical staging.

Objective 2

To investigate factors associated with non-adherence to ART in peripheral (rural) settings in order to provide data for public health interventions.

Specific objectives

1. To identify factors associated with non-adherence to ART in rural and semi-urban settings of Tanzania

Objective 3

To document experiences and lessons generated in the process of implementing ART care and treatment at a health centre in resource limited settings.

1. To study HIV and AIDS case management in a rural health centre
2. To describe experiences in the process of implementing ART in a rural health centre
3. To identify and share lessons learned during ART services delivery at a rural health centre.

4.2 Study area, research approach and principal methods

4.2.1 Study area

The studies were conducted at Tumbi Regional Hospital and Chalinze Health Centre in Pwani Region, Eastern Tanzania between April 2008 and June 2009. Tumbi Regional Hospital is located 40 km from Dar es Salaam, the commercial capital of Tanzania. The hospital has a bed capacity of 200 beds and serves as a regional referral Hospital. Chalinze Health Centre is located 70 km from Tumbi Hospital at the junction of the main upcountry highways with an HIV prevalence of 15%, whereas the prevalence in Pwani Region was 7%. Both heath facilities provide services to a mixture of patients from semi-urban and rural villages. Most residents of Chalinze reside in rural villages and generate income from farming and trading of different types of goods.

Tumbi Hospital runs two separate HIV/AIDS clinics for adults and children. At the time of initiation of this study in April 2008, Tumbi Hospital had enrolled a total of 3851 and Chalinze Health Centre had enrolled a total of 450 patients to care and treatment. Chalinze Health Centre HIV/AIDS care and treatment clinics started services in May 2007.

4.2.2 Research approach and methods

The research consisted of three sub-studies carried out consecutively utilizing different study designs and populations.

Objective 1:

To investigate challenges of HIV and AIDS case management related to changing HIV-clinical manifestation and parasitic co-infections in rural and semi-urban settings and propose measures to improve HIV-infected patient care.

The approach: This was a longitudinal and descriptive study design and used a structured clinical report form adopted from the Ifakara clinical surveillance system and IMCI (for children) was used by the attending clinician (Principal investigator and the assistant clinician) to document patient disease history, clinical features, diagnosis, laboratory investigation and treatment.

Objective 2:

To investigate factors associated with non-adherence to ART in a rural setting in order to provide data for public health intervention.

The approach

A case-control study was carried out at Tumbi Hospital and Chalinze Health centre. A structured questionnaire was used to assess adherence to doses, food instruction and time schedule. Patients with less than 95% adherence to time schedule; dose and food were defined as non-adherence cases. Patients with 100% adherence became controls. A structured questionnaire containing factors known to be associated with non-adherence to ART in similar settings was administered. Univariate and multivariate conditional logistic regression were performed to identify factors associated with non-adherence.

Objective 3:

To document experiences and lessons generated in the process of implementing ART care and treatment at a health centre in a resource limited setting.

The approach: This was a cross sectional study carried out to study patients registered between May 2007 to 31April 2009. Two different methods of data collection were used; non-participant observations of health providers' performance and retrospective pre ART and ART registers reviews.

References

1. Unaids WHO. AIDS epidemic update: December 2007. Geneva: UNAIDS. 2007;

2. Chen L, Jha P, Stirling B, Sgaier SK, Daid T, Kaul R, et al. Sexual risk factors for HIV infection in early and advanced HIV epidemics in sub-Saharan Africa: systematic overview of 68 epidemiological studies. PLoS One. 2007;2(10).

3. Hymes KB, Greene JB, Marcus A, William DC, Cheung T, Prose NS, et al. Kaposi's sarcoma in homosexual men–a report of eight cases. The Lancet. 1981; 318(8247):598–600.

4. Associated EI. Pneumocystis Pneumonia—Los Angeles.

5. Rep MM. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men–New York City and California. MMWR Morb Mortal Wkly Rep. 1981;30(25):305–8.

6. Kamradt T, Niese D, Vogel F. Slim disease (AIDS). Lancet. 2(8469-70):1425.

7. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science. 1984; 224(4648):500.

8. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983; 220(4599):868.

9. Weller I, Crawford DH, Iliescu V, MacLennan K, Sutherland S, Tedder RS, et al. Homosexual men in London: Lymphadenopathy, immune status, and Epstein-Barr virus infection. Annals of the New York Academy of Sciences. 1984;437(Acquired Immune Deficiency Syndrome):238–253.

10. Quinn TC, Mann JM, Curran JW, Piot P. AIDS in Africa: an epidemiologic paradigm. Bulletin of the World Health Organization. 2001; 79:955–963.

11. Trends C. World AIDS Day—December 1, 1993. World. 1993; 42:45.

12. Gisselquist D, Potterat JJ. Heterosexual transmission of HIV in Africa: an empiric estimate. International Journal of STD and AIDS. 2003; 14(3):162–173.

13. Steinbrook R. The AIDS epidemic in 2004. New England Journal of Medicine. 2004; 351(2):115.

14. Sepkowitz KA. AIDS–the first 20 years. The New England journal of medicine. 2001; 344(23):1764.

15. Lugalla J, Emmelin M, Mutembei A, Sima M, Kwesigabo G, Killewo J, et al. Social, cultural and sexual behavioural determinants of observed decline in HIV infection trends: lessons from the Kagera Region, Tanzania. Social science & medicine. 2004; 59(1):185–198.

16. Mabumba ED, Mugyenyi P, Batwala V, Mulogo EM, Mirembe J, Khan FA, et al. Widow inheritance and HIV/AIDS in rural Uganda. Tropical doctor. 2007; 37(4):229.

17. Jochelson K, Mothibeli M, Leger JP. Human immunodeficiency virus and migrant labor in South Africa. International Journal of Health Services. 1991; 21(1).

18. Hunter DJ. AIDS in sub-Saharan Africa: the epidemiology of heterosexual transmission and the prospects for prevention. Epidemiology. 1993; 4(1):63–72.

19. Alonso A, de Irala J, Rifkin W. Strategies in HIV prevention: the ABC approach. Lancet. 2004; 364(9439):1033.

20. Women MH. The ABCs of HIV Prevention. 2003;

21. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev. 2002; 1:D003255.

22. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with Zidovudine treatment. The New England Journal of Medicine. 1994; 331(18):1173.

23. Vlahov D, Junge B. The role of needle exchange programs in HIV prevention. Public Health Rep. 1998 Jun; 113(Suppl 1):75-80.

24. Puro V, Cicalini S, Carli GD, Soldani F, Antunes F, Balslev U, et al. Post-exposure prophylaxis of HIV infection in healthcare workers: recommendations for the European

setting. European journal of epidemiology. 2004; 19(6):577–584.

25. Winston A, McAllister J, Amin J, Cooper DA, Carr A. The use of a triple nucleoside-nucleotide regimen for non occupational HIV post-exposure prophylaxis. HIV medicine. 2005; 6(3):191–197.

26. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. The Lancet. 2007;369(9562):657–666.

27. Arno PS, Feiden K. Against the odds: The story of AIDS drug development, politics, and profits. HarperCollins; 1992.

28. Weber J, Desai K, Darbyshire J, others. The development of vaginal microbicides for the prevention of HIV transmission. PLoS medicine. 2005; 2(5).

29. Ho DD, Huang Y. The HIV-1 vaccine race. Cell. 2002; 110(2):135–138.

30. UNAIDS W. AIDS epidemic update: December 2005. Gèneve: UNAIDS, WHO. 2005;

31. Simon V, Ho DD, Abdool Karim Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. The Lancet. 2006; 368(9534):489–504.

32. Piot P. AIDS: from crisis management to sustained strategic response. Lancet. 2006;368(9534):526–530.

33. Tacaidsnmf.pdf [Internet]. [Cited 2010 Jul 16]; Available from: http://www.tanzania.go.tz/pdf/tacaidsnmf.pdf

34. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. New England Journal of Medicine. 1987; 317(4):185.

35. Osborn JE. The Past, Present, and Future of AIDS. JAMA. 2008 Aug 6; 300(5):581-583.

36. Van Praag E, Fernyak S, Katz AM. The implications of antiretroviral treatments. Informal Consultation April; 1997.
37. Reeves JD, Piefer AJ. Emerging drug targets for antiretroviral therapy. Drugs. 2005; 65(13):1747–1766.

38. Teixeira PR, Vitória MA, Barcarolo J. Antiretroviral treatment in resource-poor settings: the Brazilian experience. Aids. 2004; 18:S5.

39. artadultguidelines.pdf [Internet]. [Cited 2010 Jul 16]; Available from: http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

40. Tz Clinical Guidelines for ART-2005.pdf [Internet]. [Cited 2010 Jul 16]; Available from: http://www.tanzaniahivaids.info/documents/Other%20Resource%20Documents/Tz%20Clinical%20Guidelines%20for%20ART-2005.pdf

41. Scott J, Bansi L, Ivens D. HIV test uptake after introducing an opt-out screening system. International journal of STD & AIDS. 2006; 17(3):213.

42. Mocroft A, Lundgren JD. Starting highly active antiretroviral therapy: why, when and response to HAART. Journal of Antimicrobial Chemotherapy. 2004; 54(1):10.

43. FullreportJune2005.pdf [Internet]. [Cited 2010 Jul 16]; Available from: http://www.who.int/3by5/fullreportJune2005.pdf

44. WHO | Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults [Internet]. [Cited 2010 Jul 16]; Available from: http://www.who.int/hiv/pub/plhiv/ctx/en/index.html

45. Calmy A, Pinoges L, Szumilin E, Zachariah R, Ford N, Ferradini L. Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort. Aids. 2006; 20(8):1163.

46. Robertson J, Meier M, Wall J, Ying J, Fichtenbaum CJ. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. Clinical Infectious Diseases. 2006; 42:1639–1646.

47. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, et al. Antiretroviral Therapy in Lower Income Countries (ART-LINC) collaboration. ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. 2006;367(9513):817–824.

48. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. Aids. 2004;18(12):1615.

49. Kim AA, Wanjiku L, Macharia DK, Wangai M, Isavwa A, Abdi H, et al. Adverse Events in HIV-Infected Persons Receiving Antiretroviral Drug Regimens in a Large Urban

Slum in Nairobi, Kenya, 2003-2005. J Int Assoc Physicians AIDS Care (Chic Ill). 2007; 6(3):206-9.

50. Moh R, Danel C, Sorho S, Sauvageot D, Anzian A, Minga A, et al. Haematological changes in adults receiving a Zidovudine containing HAART regimen in combination with co-trimoxazole in Côte d'Ivoire. Antivir Ther. 2005; 10(5):615–24.

51. Kumarasamy N, Vallabhaneni S, Cecelia AJ, Yepthomi T, Balakrishnan P, Saghayam S, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2006; 41(1):53.

52. Lyamuya E, Bredberg-R\aadén U, Massawe A, Urassa E, Kawo G, Msemo G, et al. Performance of a modified HIV-1 p24 antigen assay for early diagnosis of HIV-1 infection in infants and prediction of mother-to-infant transmission of HIV-1 in Dar es Salaam, Tanzania. JAIDS Journal of Acquired Immune Deficiency Syndromes. 1996; 12(4):421.

53. Egger M, May M, Chêne G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies*. The Lancet. 2002;360(9327):119–129.

54. Ferradini L, Laureillard D, Prak N, Ngeth C, Fernandez M, Pinoges L, et al. Positive outcomes of HAART at 24 months in HIV-infected patients in Cambodia. Aids. 2007; 21(17):2293.

55. Chan KCW, Wong KH, Lee SS. Universal decline in mortality in patients with advanced HIV-1 disease in various demographic subpopulations after the introduction of

HAART in Hong Kong, from 1993 to 2002. HIV medicine. 2006; 7(3):186–192.

56. Murri R, Lepri AC, Cicconi P, Poggio A, Arlotti M, Tositti G, et al. Is moderate HIV viremia associated with a higher risk of clinical progression in HIV-infected people treated with highly active antiretroviral therapy: evidence from the Italian cohort of antiretroviral-naive patients study. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2006; 41(1):23.

57. F\ätkenheuer G, Theisen A, Rockstroh J, Grabow T, Wicke C, Becker K, et al. Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients. Aids. 1997; 11(14):F113.

58. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Annals of Internal Medicine. 1999; 131(2):81.

59. Ramadhani HO, Thielman NM, Landman KZ, Ndosi EM, Gao F, Kirchherr JL, et al. Predictors of incomplete adherence, virologic failure, and antiviral drug resistance among HIV-infected adults receiving antiretroviral therapy in Tanzania. Clinical Infectious Diseases. 2007; 45:1492–1498.

60. tuapr_2009_en.pdf [Internet]. [Cited 2010 Aug 30]; Available from: http://www.who.int/hiv/pub/tuapr_2009_en.pdf

61. Stoeckle M, Mchomvu R, Hatz C, Battegay M, Aris EA, Mshinda H, et al. Moving up from 3 by 5. The Lancet Infectious Diseases. 2006 Aug; 6(8):460-461.

62. Cambiano V, Lampe FC, Rodger AJ, Smith CJ, Geretti AM, Lodwick RK, et al. Use of a prescription-based measure of antiretroviral therapy adherence to predict viral rebound in HIV-infected individuals with viral suppression. HIV Medicine. 2010; 11(3):216-224.

63. Gordillo V, del Amo J, Soriano V, González-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. Aids. 1999; 13(13):1763.

64. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clinical Infectious Diseases. 2003; 37:1112–1118.

65. Piacenti FJ. An update and review of antiretroviral therapy. Pharmacotherapy. 2006; 26(8):1111–1133.

66. Nilsson Sch\önnesson L, Williams ML, Ross MW, Bratt G, Keel B. Factors associated with suboptimal antiretroviral therapy adherence to dose, schedule, and dietary instructions. AIDS and Behaviour. 2007; 11(2):175–183.

67. El-Sadr W, Neaton J. Episodic CD4-guided use of ART is inferior to continuous therapy: Results of the SMART study. In: 13th Conference on Retroviruses and Opportunistic Infections. 2006.

68. Kaplan JE, Hu DJ, Holmes KK, Jaffe HW, Masur H, De Cock KM. Preventing opportunistic infections in human immunodeficiency virus-infected persons: implications for the developing world. The American journal of tropical medicine and hygiene. 1996; 55(1):1-11.

69. Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons–2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR Recomm Rep. 2002;51(RR-8):1-52.

70. Masur H, Holmes KK, Kaplan JE. Introduction to the 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Clin Infect Dis. 2000; 30 Suppl 1:S1-4.

71. Harms G, Feldmeier H. The impact of HIV infection on tropical diseases. Infectious disease clinics of North America. 2005; 19(1):121-35, ix.

72. Kamya MR, Gasasira AF, Yeka A, Bakyaita N, Nsobya SL, Francis D, et al. Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: a population-based study. J Infect Dis. 2006; 193(1):9-15.

73. Grant AD, Djomand G, Smets P, Kadio A, Coulibaly M, Kakou A, et al. Profound immunosuppression across the spectrum of opportunistic disease among hospitalized HIV-infected adults in Abidjan, Cote d'Ivoire. AIDS (London, England). 1997; 11(11):1357-64.

74. Morgan D, Malamba SS, Orem J, Mayanja B, Okongo M, Whitworth JA. Survival by AIDS defining condition in rural Uganda. Sex Transm Infect. 2000; 76(3):193-7.

75. Secor WE. Interactions between Schistosomiasis and infection with HIV-1. Parasite immunology. 2006; 28(11):597-603.

76. Borkow G, Leng Q, Weisman Z, Stein M, Galai N, Kalinkovich A, et al. Chronic immune activation associated with intestinal helminth infections results in impaired signal transduction and anergy. The Journal of clinical investigation. 2000; 106(8):1053-60.

77. Fraziano M, Cappelli G, Santucci M, Mariani F, Amicosante M, Casarini M, et al. Expression of CCR5 is increased in human monocyte-derived macrophages and alveolar macrophages in the course of in vivo and in vitro Mycobacterium tuberculosis infection. AIDS research and human retroviruses. 1999; 15(10):869.

78. Hughes GJ, Willey SJ, Cochrane A, Leen C, Bell JE, Simmonds P. Virus immunocapture provides evidence of CD8 lymphocyte-derived HIV-1 in vivo. AIDS (London, England). 2007; 21(12):1507-13.

79. Holmes CB, Losina E, Walensky RP, Yazdanpanah Y, Freedberg KA. Review of human immunodeficiency virus type 1-related opportunistic infections in sub-Saharan Africa. Clin Infect Dis. 2003; 36(5):652-62.

80. French N, Nakiyingi J, Lugada E, Watera C, Whitworth JA, Gilks CF. Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. AIDS (London, England). 2001; 15(7):899-906.

81. Germani Y, Minssart P, Vohito M, Yassibanda S, Glaziou P, Hocquet D, et al. Etiologies of acute, persistent, and dysenteric diarrhoeas in adults in Bangui, Central African Republic, in relation to human immunodeficiency virus serostatus. The American journal of tropical medicine and hygiene. 1998; 59(6):1008.

82. Atzori C, Bruno A, Chichino G, Cevini C, Bernuzzi AM, Gatti S, et al. HIV-1 and parasitic infections in rural Tanzania. Ann Trop Med Parasitol. 1993 Dec; 87(6):585-593.

83. WHO, Mahe &, Mayanja &, Whitworth &, [[WHO]]. Interim proposal for a WHO Staging System for HIV infection and Disease. Wkly Epidemiol Rec. 1990; 65(29):221–224.

84. Marques N, Cabral S, Sa R, Coelho F, Oliveira J, Saraiva da Cunha JG, et al. [Visceral leishmaniasis and HIV infection in the HAART era]. Acta medica portuguesa. 2007; 20(4):291-8.

85. Dismukes WE. Cryptococcal meningitis in patients with AIDS. J Infect Dis. 1988;157(4):624-8.

86. Bentwich Z, Maartens G, Torten D, Lal AA, Lal RB. Concurrent infections and HIV pathogenesis. AIDS (London, England). 2000; 14(14):2071-81.

87. Gilks CF, Brindle RJ, Mwachari C, Batchelor B, Bwayo J, Kimari J, et al. Disseminated Mycobacterium avium infection among HIV-infected patients in Kenya. JAIDS Journal of Acquired Immune Deficiency Syndromes. 1995; 8(2):195.

88. von Reyn CF, Arbeit RD, Tosteson AN, Ristola MA, Barber TW, Waddell R, et al. The international epidemiology of disseminated Mycobacterium avium complex infection in AIDS. AIDS. 1996; 10(9):1025.

89. Lipman M, Breen R. Immune reconstitution inflammatory syndrome in HIV. Current Opinion in Infectious Diseases. 2006; 19(1):20.

90. Salami AK, Olatunji PO, Oluboyo PO. Spectrum and prognostic significance of opportunistic diseases in HIV/AIDS patients in Ilorin, Nigeria. West Afr J Med. 2006; 25(1):52-6.

91. Tirwomwe JF, Rwenyonyi CM, Muwazi LM, Besigye B, Mboli F. Oral manifestations of HIV/AIDS in clients attending TASO clinics in Uganda. Clin Oral Investig. 2007; 11(3):289-92.

92. Lian YL, Heng BS, Nissapatorn V, Lee C. AIDS-defining illnesses: a comparison between before and after commencement of highly active antiretroviral therapy (HAART). Curr HIV Res. 2007; 5(5):484-9.

93. Serwadda D, Sewankambo NK, Carswell JW, Bayley AC, Tedder RS, Weiss RA, et al. Slim disease: a new disease in Uganda and its association with HTLV-III infection. The Lancet. 1985; 326(8460):849–852.

94. EFS2006_TZ.pdf [Internet]. [Cited 2010 Jul 16]; Available from: http://apps.who.int/globalatlas/predefinedReports/EFS2006/EFS_PDFs/EFS2006_TZ.pdf

95. HIVCP_TZA.pdf [Internet]. [Cited 2010 Jul 16]; Available from: http://www.who.int/hiv/HIVCP_TZA.pdf

96. Schutz R, Savarit D, Kadjo JC, Batter V, Kone N, La Ruche G, et al. Excluding blood donors at high risk of HIV infection in a west African city. British Medical Journal. 1993; 307(6918):1517.

97. 36287.pdf [Internet]. [Cited 2010 Jul 16]; Available from: http://www.state.gov/documents/organization/36287.pdf

98. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. The Lancet. 2006; 368(9534):505–510.

99. Harries A, Nyangulu D, Hargreaves N, Kaluwa O, Salaniponi F. Preventing antiretroviral anarchy in sub-Saharan Africa. The Lancet. 2001 Aug 4;358(9279):410-414.

100. Loewenson R, McCoy D. Access to antiretroviral treatment in Africa. British Medical Journal. 2004; 328(7434):241.

101. Hanson K, Ranson MK, Oliveira-Cruz V, Mills A. Expanding access to priority health interventions: a framework for understanding the constraints to scaling-up. Journal of International Development. 2003; 15(1):1–14.

102. Hanson S, Thorson A, Rosling H, Örtendahl C, Hanson C, Killewo J, et al. Estimating the Capacity for ART Provision in Tanzania with the Use of Data on Staff Productivity and Patient Losses. PLoS ONE. 4(4).

103. Meyers T, Moultrie H, Naidoo K, Cotton M, Eley B, Sherman G. Challenges to pediatric HIV care and treatment in South Africa. The Journal of infectious diseases. 2007; 196:S474–S481.

104. McCoy D, Chopra M, Loewenson R, Aitken J, Ngulube T, Muula A, et al. Expanding Access to Antiretroviral Therapy in Sub-Saharan Africa: Avoiding the Pitfalls and Dangers, Capitalizing on the Opportunities. Am J Public Health. 2005 Jan 1;95(1):18-22.

105. Declaration A. Abuja declaration on HIV/AIDS, tuberculosis, and other related infectious diseases. Retrieved November. 2001; 13:2007.

106. Morrison JS. Expanding antiretroviral treatment in developing countries creates critical new challenges. Centre for strategic and international studies HIV/AIDS task force report. 2002;

107. Harms G, Feldmeier H. HIV infection and tropical parasitic diseases - deleterious interactions in both directions? Trop Med Int Health. 2002; 7(6):479-88.

Figure 5.1: Patients at Tumbi HIV/AIDS Clinic

Part III

Papers

Chapter 5: Parasitic co-infection and their effects on CD4 +T-lymphocytes and clinical parameters of adult HIV-1 patients in Tanzania

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Abstract

Background

Untreated tropical parasitic co-infections appear to fasten the progression of HIV-1 disease. However, there have been few studies to ascertain the interference of parasitic co-infection in resource limited settings where HIV/AIDS management largely depend on CD4+T cells counts and WHO clinical staging. This study, therefore, aimed to determine the prevalence of parasites and their association with CD4+Tcells changes and clinical classification of HIV-infection in patients attending care and treatment in Tanzania.

Methods

Adult HIV-infected patients registering for the first time at HIV/AIDS clinics were recruited; physical examination and laboratory tests were performed at baseline and after 6th months. Patients were assigned a clinical stage and screened for helminths and *Plasmodium sp*. co-infection, CD4+Tcells, haemoglobin and HIV-1 p24 antigen.

Results

Of the 421 HIV-1 infected patients studied, 198 (47.0%) were co-infected with one or more parasites. While 93/421(22.1%) patients had helminths only co-infection, and 50/421(12.9%) had *Plasmodium sp* only co-infection. Mixed *Plasmodium sp* and helminths co-infection was diagnosed in 55/421(13.0%) patients. Helminths frequently diagnosed included hookworm 65/421(15.4%), Schistosomiasis 49/421(11.6%), *Strongyloides stercoralis* 57/421(13.5%), and *Ascaris lumbricoides* 54/421(12.8%). There was no statistical associations between CD4^{+}Tcells <200/µl, or WHO clinical stage III/IV with parasites co-infections (AOR 1.2, 95%CI 0.8-1.8). Anaemia was common in parasite co-infected patients (32.8% vs 18.8%). Parasites co-infection was associated with risk of anaemia (AOR 2.1, 95%CI

1.3-3.2). In multivariable logistic regression analysis, baseline CD4+Tcells <200/µl was significantly (AOR 2.4, 95%CI 1.3-4.7) associated with CD4+Tcells <200/µl at six months. HIV-1 P24 antigen mean concentration was higher in parasites co-infected patients (ranges 47.6 to 56.9) compared to patients without parasites co-infection (5.5).

Conclusions

We have looked at one set of parasites and found high prevalence of malaria and helminths co-infection in HIV-infected individuals. Given the available reports on health impacts of helminths co-infection in HIV/AIDS patients and the anecdotal reports of helminths health effects even in HIV-uninfected persons, helminths and other prevalent parasites should not be ignored in HIV/AIDS programs. And based on local helminths epidemiology and HIV-infected cohort specific helminths co-infection prevalence data, mass treatment of soil transmitted helminths can be confidently incorporated in HIV/AIDS care and treatment programs.

Introduction

HIV-infection and AIDS in sub-Saharan Africa present with diverse clinical characteristics reflecting the variety of prevalent endemic diseases within each area. More than 100 different disease-causing agents are found in the tropics, including viruses, bacteria, fungi, protozoa, helminths and arthropods (1). A relatively small proportion of these pathogens cause the majority of serious health effects to HIV-infected persons (2). Distribution of these pathogens is geographically sensitive to favourable environments characterized by social behaviours and ecological factors affecting the risk of their transmission (3).

Concurrence of HIV and tropical infections affect each other mutually. HIV-infection in patients with parasites infection alters the natural history of parasites diseases pathogenesis, impede

rapid diagnosis, or reduce the efficacy of anti-parasitic treatment (4) (5). HIV-1 compromises the cellular immune system through destroying CD4+Tcells and macrophages (6) thus reducing the immune system's ability to resist infection from endemic pathogens (7). HIV-infected persons are susceptible to new infection and reactivation of (6) latent infections (1). As result, HIV-immunosuppression facilitates infections, increases the severity of infection, changes disease presentation and complicates treatment (8). Of particular importance is the increased risk of parasitaemia and clinical malaria semi immune HIV-infected adults in endemic malaria regions (9).

In addition to HIV-effects on susceptibility and pathogenesis of tropical diseases, people living with tropical infections are at increased risk for HIV-infection and unfavourable disease progression (10).

Health effects of parasitic co-infections in HIV-infected persons marked HIV/AIDS clinical manifestations in the early decades of HIV epidemic. For example, protozoa infections caused chronic diarrhoea which resulted into wasting (slim disease), chronic fever without an obvious source, and pulmonary disease syndromes which marked AIDS in sub Saharan Africa (11) (2). There is evidence that helminths species specifically alter HIV disease progression. Interaction of Schistosome and HIV-infections with host CD4+Tcells leads to bi-directional effects which are different from sequelae caused by either infectious agent alone (12). Helminths infections lead to greater HIV-replication and disease progression through immune activation of cellular mechanisms which renders the CD4+Tcells susceptible to HIV-infection resulting into increased viral load (13). High viral load is associated with rapid CD4+Tcells death and disease progression to AIDS (14). Untreated *Strongyloides stercoralis* causes hyper-infection syndrome in immunosuppressed patients during the early stages of immune recovery after initiation of antiretroviral therapy (ART). It is difficult to distinguish between the clinical

manifestation of strongyloidiasis hyper-infection syndrome is distinguished and the immune-reconstitution syndrome induced by HAART in patients with CD4+Tcells <200/µl; both conditions are fatal without proper management (15)] (16)]. Ascariasis is associated with CD4+Tcells <200/µl, an effect which is reversed by Albendazole treatment (17). Other complications of helminths and malaria in HIV-infected persons include aggravation of diarrhoea, anaemia and fever symptoms (18).

Although scientists still debate on the survival benefit of routine screening and treatment for helminths and other parasitic infection in HIV-infected patients, helminths and malaria infections continue to cause morbidity and aggravated mortality (9). Treatment of parasitic infections could provide an immediate benefit in areas where both HIV-1 and helminths are prevalent.

Tanzania has overlapping high prevalence rates of HIV and parasitic infections (19). Scaling up of HIV and AIDS care and treatment services have become well-established and widely available, so quality of care becoming increasingly important and co-infections with latent helminths and malaria an important area to investigate.

Monitoring of HIV-infected patients in resource limited settings depends on clinical presentation and CD4+Tcells measurements. However, there have been few studies to ascertain the interference of parasites co-infection on CD4+Tcells and clinical monitoring of HIV-infected patients. This study, therefore, aimed to determine the prevalence of parasites and their association with CD4+Tcells changes and clinical classification of HIV-infection in patients attending care and treatment in Tanzania.

Methods

Study design

Between April 2008 and March 2009, we studied HIV-infected adult patients residents of catchments areas of Tumbi Hospital and Chalinze Health Centre, both located in rural and peri-urban areas outside of Dar es Salaam, Tanzania. Newly enrolled HIV-infected patients attending care and treatment services were eligible for the study. Exclusion criteria were age under 18 years, pregnancy, and patients with obvious severe disease conditions like Tuberculosis, Cryptococcus Meningitis, Pneumonia and generalized Kaposi's sarcoma, or imminent transfer to another clinic.

A study nurse identified eligible patients after completing routine clinic registration procedures. Patients were individually screened for eligibility after presenting key facts involved in the study; thereafter a standardized informed consent was administered. Consenting patients were assigned a study identification number which was affixed on their clinic card and case file. The patient was then referred to study clinician for clinical examination.

Study clinicians recorded patients' clinical history, performed physical examinations and staging according to the Tanzania and WHO clinical guidelines for management of HIV and AIDS. Patients were referred to the laboratory for samples collection. Blood specimens were collected in EDTA tubes for enumeration of CD4+Tcells, haemoglobin and malaria smear, part of the sample was frozen and shipped to Ifakara Health Institute laboratory for HIV-1 P24 plasma ELISA assays.

Fresh stool samples were collected in sterilized plastic containers, and preserved in 10% formalin and were examined within 24 hours by formol-ether concentration techniques (20). Stool samples found to contain ova or larvae, intensity of infection were estimated by quantitative analysis of the egg burden,

according to the Kato-Katz thick-smear technique. Patients who could not produce stool on the spot were provided with sterile plastic containers and asked to bring fresh stool specimen on their next clinic visit. Sterile plastic containers were also used to collect clean-catch urine specimen.

Malaria, urine and haemoglobin results were availed to the patient on the same day; other test results were available on the follow up visits. Study patients were scheduled follow up visit 14 days after initial contact to complete ART eligibility counselling and other assessments.

Patients received standard treatments according to infections diagnosed: malaria was treated using Coartem ((artemether 20 mg/lumefantrine 120 mg), intestinal helminths were treated with Albendazole (400mg day one and 200mg 2 subsequent days), and Schistosomiasis was treated with Praziquantel (40mg/kg divided into 2 doses 6 hours apart).

After the 14th day contact, study patients were scheduled to monthly follow up visits regardless of their ART status. A date for the 6th month follow up visit was communicated to patients during their subsequent clinic visits. Clinical examination and laboratory procedures performed at initial contact were repeated at the 6th month visit.

Laboratory procedures

Specimens for CD4+Tcells, haemoglobin, malaria, sputum, urine and stool samples were analyzed at Tumbi Hospital laboratory. CD4+Tcells analysis was performed using automated FACS count (BD Biosciences, California, USA). Biochemistry and haematological parameters were analyzed using Biochemical analyzer (Italy) and haematological analyzer (Pentra 80, France) respectively. Malaria smears were Giemsa stained and microscopically examined for parasitaemia. Sputum specimens were stained using Ziehl-Neelsen technique and examined for mycobacterium tuberculosis.

Stool samples were fixed using sodium acetate-acetic acid-formalin (SAF) solution and microscopically examined for parasites and helminths. Part of freshly passed stool was cultured in Xylose Lysine Deoxycholate Agar (XLD) media for Salmonella and Shigella species. Direct microscopic examination was performed on urine samples. HIV-1 P24 sample analysis was carried out based on the Ifakara Health Institute adapted PerkinElmer Life Sciences's "P24 Ultra sensitive Assay Protocol" (ELAST® kit) (21)].

Data analysis

Data was entered into Microsoft ®Access, and analyzed using Stata Intercooled version 9. Standard definitions of severe immunological suppression were used in terms of the magnitude of CD4+Tcells decline. Patients with CD4+Tcells below and above 200 cells/µl were categorized as severely and moderately immunosuppressed. Logistic regression models were used to generate odds ratios associated with CD4+Tcells <200/µl. An attempt was made to compare patient groups according to their species specific helminths infection but small samples sizes constraints limited the ability to draw statistical inferences.

Ethical approval

The study received scientific and ethical approval from the Muhimbili University of Health and Allied Sciences Research Ethics Review Board (Ref.No.MU/RP/AEC/Vol.XII/58) Permission was granted by Region, District and hospital authorities. Informed consent for participation was obtained from patients using Kiswahili language.

Results

A total of 464 subjects were enrolled into the study between April 2008 and March 2009, 421 patients provided complete baseline data for analysis. Forty three patients were excluded from the analysis because of insufficient samples for

parasitological diagnosis. Patients excluded did not differ from the remaining patients in terms of socio-demographic characteristics, CD4 cell counts and clinical presentation at the time of enrolment.

Baseline characteristics

The mean age of participants was 35.7 (SD 34.6 to 36.9) and the mean body weight was 51.6(SD 50.0 to 53.1). Women were the majority of patients 261/421(62%). In total 272/421 (64.6%) of patients were living in rural areas and a high proportion of all patients had primary education 336/421 (80%) with no remarkable differences between patient groups. The majority of patients used pit latrine for excreta disposal and obtained water for domestic use from mixed sources (Table 5 1).

Among the 421 HIV-1 infected patients enrolled with complete data for analysis at initial assessment, 198 (47%) were found to be co-infected with one or more parasites. Helminths-only co-infection was diagnosed in 93/421 (22.1%) patients, while 50/421 (11.9%) patients exhibited Plasmodium sp. parasitaemia but no helminths co-infection. Mixed Plasmodium sp and helminths co-infection was diagnosed in 55/421 (13.1%) patients (Table 5 1Table 5 1: Baseline demographic, social and clinical characteristics of patients by parasites status attended at Tumbi Hospital and Chalinze Health Centre between April 2008 and March 2009

Plasmodium sp was the most common parasite isolated 105/421(24.9%). Of the helminths diagnosed, most frequently detected were: hookworm 65/421(15.4%), Schistosomas 49/421(11.6%), *Strongyloides stercoralis* 57/421(13.5%), and *Ascaris lumbricoides* 54/421(12.8%). Parasites infected patients harboured one and up to five types of parasites. Multiple parasites were diagnosed in 89/421(21.1%) patients. Only one patient was found to harbour all five parasites (Table 5 2).

At the time of enrolment into the study, more than half of the

patients were in clinical stages III/IV and had CD4+Tcells <200/µl (237/421(56.3%) and 248/421(58.9%) respectively). The mean HIV-1 p24 concentration was 15.3 (SD 20.3). A higher HIV-1 p24 concentration was found in patients with lower CD4 cell counts and WHO clinical stages III/IV. An additional finding was the high concentration of HIV-P24 antigens in patients with parasites co-infection (Helminths 47.6pg/ml, Malaria 49.7pg/ml and mixed helminths /malaria 56.9pg/ml) compared to patients without parasites (5.5pg/ml). High concentration of HIV-1 P24 is associated with rapid HIV-1 disease progression.

Effect of parasites co-infection on CD4+Tcells, anaemia and WHO clinical stages

Overall, parasites infected patients had lower CD4 cell counts than parasites free patients, but this was not statistically significant (Table 5 3). Multiple infection was associated with CD4+Tcells <200/µl (1 vs. 2 parasites: OR 1.9, 95%CI 1.2-3.5; 1 vs. 3-5 parasites: OR 2.3, 95%CI 1.5-10.7) than one parasite co-infection. The test for trend across ordered groups provided consistently some evidence that the number of parasites is associated with low CD4+Tcells counts. However, the result was only marginally significant (Z = 1.69, p=0.09) (Table 5 2).

The associations of CD4+Tcells <200/µl, anaemia (haemoglobin<8.0g/dl) and WHO clinical stage III/IV were examined in patients with and without parasites co-infections (Table 5 3). No statistical significant differences were observed between patients with and without parasites co-infection in association with CD4+Tcells <200/µl. The adjusted odds ratios for parasites co-infected patients were less than one, except for patients with mixed malaria and helminths, any helminths, strongyloides and *Ascaris lumbricoides* only infections (OR=1.2, 1.6, 1.5 and 2.2 respectively).

The prevalence of anaemia was higher 64/198(32.5%) in parasite co-infected compare to 42/223(18.8%) in patients without co-

infection. Parasites co-infection was associated with significant risk of anaemia (AOR 2.1, 95%CI 1.3 to 3.2). The odds of having anaemia were high in patients with mixed helminths and malaria infection, increased by a factor of more than 3 (AOR=3.8, 95% CI 1.9 to 7.1) compared to patients without co-infection. There was a strong association between *Ascaris lumbricoides* and anaemia (AOR=5.3, 95%CI 1.8 to 15.7). Patients with any of the helminths infection had almost two times higher odds of having anaemia (AOR 1.9, 95%CI (1.1-3.3). Similarly, patients co-infected with hookworm had two times higher odds (AOR=2.1, 95% CI 0.9-6.7) to have severe anaemia; however, this association was not statistically significant. The associations between either *Strongyloides stercoralis* or Schistosomiasis and anaemia were affected by small samples and did not demonstrate any statistically significant association with anaemia (AOR 0.4, 95%CI 0.1-2.9, AOR 0.9, 95%CI 0.2-4.5 respectively). However, it is known that *Schistosoma haematobium* causes moderate anaemia. Neither multiple co-infection with any parasites (AOR 1.2, 95%CI 0.8-1.8) nor with single infection (AOR 0.8-1.7, 95% CI 0.4-5.2) was significantly associated with WHO clinical stages III/IV.

Changes in CD4+Tcell counts after treatment

Of the 421 patients for whom complete data were available at baseline analysis, one patient died and 18 patients were infected or re-infected with parasites during the 6 months follow-up period. At the end of 6 months follow-up, 196 (98.9%) of those with parasites and 222 (99.6%) of those without parasites at enrolment were attended and had complete data for analysis. In total 312(74.1%) patients were started on ART during the period.

We observed an increase in CD4+Tcell counts at six months on majority of ART patients with and those without parasites (Table 5 4). Patients with parasites at baseline 151/196(77.0%) experienced increase in CD4+Tcell counts, the majority of whom

were those with ART treatment 129/151(85.4%). Similarly, for patients without parasites co-infection, 147/222(66.2%) had CD4+Tcell counts increased and majority 125/147 (85.0%) were patients on ART treatment. The mean CD4+Tcell counts increase was 111.6(9.0) and 108.6(8.2) in patients with and without parasite infection at baseline respectively.

The CD4+Tcell counts decreased between enrolment and 6 months follow-up in 45/196(22.9%) and 75/222(33.7%) patients with and without parasites, respectively. The mean CD4+Tcell counts decrease was 109.3(SD 14.9) and 101.2(SD 29.9) in patients with and without parasites, respectively.

Statistical significant difference was observed between patients with parasites co-infection who experienced CD4+Tcell counts increase and those whose CD4+Tcell counts decreased (p=0.001). Similar results were observed in patients without parasites.

Variables known to be associated with CD4 cell count changes, were included in multivariable logistic regression analysis, baseline CD4+Tcells <200/µl was significantly (AOR 2.4, 95%CI 1.3-4.7) associated with CD4+Tcells <200/µl at six months (Table 5 5). New infections with helminths or malaria were not associated with CD4+Tcells <200/µl at six months (AOR 1.6, 95% CI 0.4-5.7). This is probably because of low parasite infection intensity to impact on CD4+ T-cell changes within the follow up period. The impact of P24 and WHO clinical stages in predicting CD4+Tcells <200/µl at six months was obviously influenced by the initiation of ART (AOR 1.0, 95% CI 0.7 to 1.6).

Discussion

This study found malaria and helminths co-infection more frequent in HIV-infected patients than other parasites. The prevalence rate of helminths was 22.1% lower than study findings in other sub-Saharan African settings(22) (23) but higher than

results from studies in other rural Tanzania (24) (25). We isolated frequently hookworm, *A. lumbricoides,* and *Strongyloides stercoralis* in patients with CD4-T cells<200 µ/l and not the common HIV-related protozoa which marked early AIDS manifestation as causes of chronic diarrhoea. These findings could be setting specific or a phenomenon of changing AIDS manifestation because previous studies have reported higher prevalence rates of *Cryptosporidium* and *Isospora belli* among HIV-infected patients (22) (26).

The prevalence of malaria co-infection in our study population was 24.9% higher than findings of previous studies in Eastern Africa (27) (9). The high malaria parasitaemia in this and other previous studies points to an important interaction between HIV-1 and malaria especially in our setting where large population of severe immunodeficiency patients and endemic malaria coexist. Malaria is known to cause transitory higher viral load while HIV-1 causes more clinical malaria, higher parasitaemia and higher rates of treatment failure in co-infected patients (5) (28).

Mixed parasites infection is common in areas where various types of parasites coexist with favourable behavioural and ecological patterns for transmission. The occurrence of polyparasitism in the current study showed an inverse relationship with CD4-T cells<200 µ/l. Health effects of polyparasitism depends on the types of parasites co-infection, mixed intestinal helminths and protozoa bring persistent diarrhoea and anaemia. Occurrence of mixed helminths and malaria infection, malaria can worsen mild anaemia due to helminths and impact on HIV-infection outcome. Although this study did show only a marginal statistically significant trend towards severe immunodeficiency as a result of polyparasitism, it highlights an important interaction especially in settings with higher prevalence of HIV-1 and parasites infection. Therefore parasites co-infection in HIV and AIDS patients should not be ignored given the availability of various reports pointing towards negative health outcomes. Site

specific assessment need to be carried out to determine the relevant and abundance of parasites to that particular area to form the bases for intervention approaches.

It is well established that CD+T-cell<200 µ/l is associated with high risk of opportunistic infection and poor disease progression (29). On the other hand parasites co-infection facilitates CD4+T-cells decline (12) through various mechanisms. This study did demonstrate a statistical significant association between multiple parasites co-infections and CD+T-cell <200 µ/l before treatment, and the odds ratios tended to show some association. Therefore, parasites co-infection increases the risk of opportunistic infection in HIV-infected patients. Then, this study finding gives the indication of a possible strong association in settings with high infection intensities and their impact on CD4+ T-cell decline.

The association of helminths and CD+T-cell <200 µ/l in this study was also affected by the low intensities of helminths infection and re-infection that occurred after treatment. An attempt was made to analyze each individual helminths species effects but the samples were insufficiently small to provide basis for inference. Parasite re-infection and failure to control for the duration of infection complicated the estimation of the true effects of helminths on CD4+ T cells decline and clinical manifestations. It is difficult to determine the duration of infection until the occurrence of CD4+Tcells decline. Cohort studies in different settings of high and low parasite prevalence intensities can provide adequate information on the specific interaction of helminths and HIV-infection. Health seeking behaviour is one of the important factors to be considered as cofounders in the role of helminths co-infection in CD4+Tcell decline. Late presentation is a common phenomenon in this setting, a majority of patients goes to seek health care after having advanced immunodeficiency. Thus, making it difficult to establish which the cause was and effect between helminths infection and CD4+Tcell decline.

Our study population consisted of patients exposed to the common known risk factors for helminths infection transmission; largely involved persons with primary level education, limited access to safe water supply; and used pit latrine, and some did not use any latrine. Therefore human faeces pollution and high rates of transmission of soil transmitted helminths is evident in this population. Improved sanitation combined with de-worming programs is likely to eliminate helminths transmission. Although the current de-worming programs are focused on school children with the highest burden of helminths infection, the prevalence of helminths in adults is also substantial because of the shift to adult population (30). Routine mass treatment in HIV-infected persons can be beneficial and provides an appropriate alternative public health approach to routine screening and treatment especially in regions with high burden of helminths.

Anaemia is a common complication which occurs in 20-80% of HIV-infected patients and is associated with rapid disease progression and mortality (31). The prevalence of anaemia in our study was significantly associated with any of the parasites co-infections. The impact of parasites co-infection on anaemia was more significant in patients with malaria and helminths polyparasitism such an association was not demonstrated in patients without parasites co-infection. HIV-infection can lead to anaemia in many ways in HIV-infected patients (32). Our results show the additive effects of parasites co-infection on other causes of anaemia in HIV-infected patients. In areas where HIV-infection, helminths and anaemia are prevalent, the interaction of anaemia and helminths or malaria in HIV-infection need to be emphasized despite of inadequate diagnosis facilities. In such settings some patients, even when HIV-replication is controlled by ART, may continue to experience poor health due to anaemia secondary to parasites infection.

Increased CD4+Tcells susceptibility to HIV-infection caused by helminths co-infection was demonstrated by finding of a strong

association between helminths co-infection and higher HIV-1 P24 antigen concentrations. This positive association can be explained by the in vivo activation of $CD4^{+}$Tcells increased susceptibility to HIV-infection and rapidly HIV-replication in helminths co-infected HIV-patients compared to helminths uninfected patients. HIV-1 P24 antigen level >5pg/ml predicts disease progression comparable to CD4+T-cells<350/µl (33), we found higher HIV-1 P24 antigen concentration in parasites co-infected patients and majority of them needed ART for survival. These findings are contrary to previous reports that showed higher viral loads in helminths free participants (34).

A noticeable increase in CD4+Tcells was recorded in both parasites co-infected and uninfected patients between enrolment and at 6 months. This change cannot be exclusively associated with treatment of helminths and malaria parasites. Our patients were given Cotrimoxazole and ARVs together with treatment of parasites. A statistical significant difference in CD4+Tcells increase was observed between the parasites co-infected and uninfected patients. This was because; a higher proportion of parasites co-infected patients had CD+T-cell <200 µ/l and started earlier ART compared to uninfected patients. Therefore, helminths or parasites co-infection treatment benefits are more expressed if combined with ART and Cotrimoxazole. Cohort studies comparing very high and very low parasite intensities in HIV-1 co-infected patients can provide useful information on the minimum essential burden of parasites responsible for CD4+ T-cells changes.

Conclusion

We have looked at one set of parasites and found high prevalence of malaria and helminths co-infection. Given the available various reports on parasites co-infection in HIV and AIDS patients, parasites should not be ignored in HIV and AIDS programs. Incorporation of these programs should not wait the

conclusion of the ongoing debate on de-worm or not de-worm. Instead, parasites co-infection in HIV-infected patients' area specific prevalence data can be used confidently to guide program approaches. In low parasite prevalence settings routine diagnostic screening is recommended and settings with high parasites prevalence mass treatment should be considered.

Competing interest

No competing interests expressed by authors.

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References

1. Karp CL, Auwaerter PG. Coinfection with HIV and tropical infectious diseases. II. Helminthic, fungal, bacterial, and viral pathogens. Clin Infect Dis. 2007;45(9):1214-20.

2. Kaplan JE, Hu DJ, Holmes KK, Jaffe HW, Masur H, De Cock KM. Preventing opportunistic infections in human immunodeficiency virus-infected persons: implications for the developing world. The American journal of tropical medicine and hygiene. 1996;55(1):1-11.

3. Masur H, Holmes KK, Kaplan JE. Introduction to the 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Clin Infect Dis. 2000;30 Suppl 1:S1-4.

4. Marques N, Cabral S, Sa R, Coelho F, Oliveira J, Saraiva da Cunha JG, et al. [Visceral leishmaniasis and HIV infection in the HAART era]. Acta medica portuguesa. 2007;20(4):291-8.

5. Kamya MR, Gasasira AF, Yeka A, Bakyaita N, Nsobya SL, Francis D, et al. Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: a population-based study. J. Infect. Dis. 2006 Jan 1;193(1):9-15.

6. Reeves JD, Piefer AJ. Emerging drug targets for antiretroviral therapy. Drugs. 2005;65(13):1747-66.

7. Hughes GJ, Willey SJ, Cochrane A, Leen C, Bell JE, Simmonds P. Virus immunocapture provides evidence of CD8 lymphocyte-derived HIV-1 in vivo. AIDS (London, England). 2007;21(12):1507-13.

8. Karp CL, Neva FA. Tropical infectious diseases in human immunodeficiency virus-infected patients. Clin Infect Dis. 1999;28(5):947-63; quiz 964-5.

9. French N, Nakiyingi J, Lugada E, Watera C, Whitworth JA, Gilks CF. Increasing rates of malarial fever with deteriorating

immune status in HIV-1-infected Ugandan adults. AIDS (London, England). 2001;15(7):899-906.

10. Bentwich Z, Maartens G, Torten D, Lal AA, Lal RB. Concurrent infections and HIV pathogenesis. AIDS (London, England). 2000;14(14):2071-81.

11. Grant AD, Djomand G, Smets P, Kadio A, Coulibaly M, Kakou A, et al. Profound immunosuppression across the spectrum of opportunistic disease among hospitalized HIV-infected adults in Abidjan, Cote d'Ivoire. AIDS (London, England). 1997;11(11):1357-64.

12. Secor WE. Interactions between schistosomiasis and infection with HIV-1. Parasite immunology. 2006;28(11):597-603.

13. Shapira-Nahor O, Kalinkovich A, Weisman Z, Greenberg Z, Nahmias J, Shapiro M, et al. Increased susceptibility to HIV-1 infection of peripheral blood mononuclear cells from chronically immune-activated individuals. AIDS (London, England). 1998;12(13):1731-3.

14. Borkow G, Bentwich Z. HIV and helminth co-infection: is deworming necessary? Parasite immunology. 2006;28(11):605-12.

15. Concha R, Harrington WJ, Rogers AI. Journal of Clinical Gastroenterology. 2005;
16. Lewthwaite P, Gill GV, Anthony Hart C, Beeching NJ. Gastrointestinal parasites in the immunocompromised. Current Opinion in Infectious Diseases. 2005;18(5):427.

17. Walson JL, Otieno PA, Mbuchi M, Richardson BA, Lohman-Payne B, Macharia SW, et al. Albendazole treatment of HIV-

1 and helminth co-infection: A randomized, double blind, placebo-controlled trial. AIDS. 2008 Aug 20;22(13):1601-1609.

18. Mbaga JM, Pallangyo KJ, Bakari M, Aris EA. Survival time of patients with acquired immune deficiency syndrome: experience with 274 patients in Dar-es-Salaam. East African medical journal. 1990;67(2):95-9.

19. Beck DL, Dogan N, Maro V, Sam NE, Shao J, Houpt ER. High prevalence of Entamoeba moshkovskii in a Tanzanian HIV population. Acta tropica. 2008;107(1):48-9.

20. Marti H, Escher E. [SAF—an alternative fixation solution for parasitological stool specimens]. Schweizerische medizinische Wochenschrift. 1990;120(40):1473-6.

21. Knuchel MC, Jullu B, Shah C, Tomasik Z, Stoeckle MP, Speck RF, et al. Adaptation of the Ultrasensitive HIV-1 p24 Antigen Assay to Dried Blood Spot Testing. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2007 3;44(3):247-253.

22. Assefa S, Erko B, Medhin G, Assefa Z, Shimelis T. Intestinal parasitic infections in relation to HIV/AIDS status, diarrhoea and CD4 T-cell count. BMC infectious diseases. 2009;9:155.

23. Modjarrad K, Zulu I, Redden DT, Njobvu L, Freedman DO, Vermund SH. Prevalence and predictors of intestinal helminth infections among human immunodeficiency virus type 1-infected adults in an urban African setting. The American journal of tropical medicine and hygiene. 2005;73(4):777-82.

24. Tarimo DS, Killewo JZ, Minjas JN, Msamanga GI. Prevalence of intestinal parasites in adult patients with enteropathic AIDS

in north-eastern Tanzania. East African medical journal. 1996;73(6):397-9.

25. Nielsen NO, Friis H, Magnussen P, Krarup H, Magesa S, Simonsen PE. Co-infection with subclinical HIV and Wuchereria bancrofti, and the role of malaria and hookworms, in adult Tanzanians: infection intensities, CD4/CD8 counts and cytokine responses. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007;101(6):602-12.

26. Kelly P, Todd J, Sianongo S, Mwansa J, Sinsungwe H, Katubulushi M, et al. Susceptibility to intestinal infection and diarrhoea in Zambian adults in relation to HIV status and CD4 count. BMC gastroenterology. 2009;9:7.

27. Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. The Lancet. 2000 Sep 23;356(9235):1051-1056.

28. Martin-Blondel G, Soumah M, Camara B, Chabrol A, Porte L, Delobel P, et al. [Impact of malaria on HIV infection.]. Med Mal Infect [Internet]. 2009 Nov 29 [cited 2010 May 13];Available from: http://www.ncbi.nlm.nih.gov/pubmed/19951829

29. Goujard C, Bonarek M, Meyer L, Bonnet F, Chaix M, Deveau C, et al. CD4 cell count and HIV DNA level are independent predictors of disease progression after primary HIV type 1 infection in untreated patients. Clin. Infect. Dis. 2006 Mar 1;42(5):709-715.

30. Eziefula AC, Brown M. Intestinal nematodes: disease burden, deworming and the potential importance of co-infection. Current opinion in infectious diseases. 2008;21(5):516.

31. Harris RJ, Sterne JA, Abgrall S, Dabis F, Reiss P, Saag M, et al. Prognostic importance of anaemia in HIV type-1-infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies. Antiviral therapy. 2008;13(8):959-67.

32. Paton NI, Sangeetha S, Earnest A, Bellamy R. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Med. 2006 Jul;7(5):323-330.

33. Schüpbach J. Viral RNA and p24 antigen as markers of HIV disease and antiretroviral treatment success. Int. Arch. Allergy Immunol. 2003 Nov;132(3):196-209.

34. Wolday D, Mayaan S, Mariam ZG, Berhe N, Seboxa T, Britton S, et al. Treatment of intestinal worms is associated with decreased HIV plasma viral load. Journal of acquired immune deficiency syndromes (1999). 2002;31(1):56-62.

Table 5. 1: Baseline demographic, social and clinical characteristics of patients by parasites status attended at Tumbi Hospital and Chalinze Health Centre between April 2008 and March 2009

Characteristics	Patients without parasites N=223	Patients with Helminths only N=93	Patients with Malaria only N=50	Mixed Helminths and Malaria N=55
Weight-kg mean(SD)	51.4(1.3)	49.2(1.2)	52.5(1.2)	48.7(1.2)
Age in years, mean(SD)	35.7(1.3)	36.0(1.3)	35.5(1.3)	34.7(1.3)
Sex n (%)				
Women	147(65.9)	51(54.8)	30(60.0)	33(60.0)
Men	76 (34.1)	42(45.2)	20(40.0)	22(40.0)
Residential status n (%)				
Rural	146 (65.5)	57(61.3)	28(56.0)	41(74.6)
Urban	77(34.5)	36(38.7)	22(44.0)	14(25.4)
Education n (%)				
Incomplete primary	28(12.6)	8(8.7)	7(14.0)	6(10.9)
Primary	173(77.6)	78(84.8)	41(82.0)	44(80.0)
College	22(9.8)	6(6.5)	2(4.0)	5(9.1)
Marital status n (%)				
Married/cohabiting	104(46.6)	35(38.0)	24(48.0)	21(38.2)
Single	66(29.6)	35(38.0)	12(24.0)	21(38.2)
Widowed	47(21.1)	16(17.4)	10(20.0)	6(10.9)
Separated/Divorced	6(2.7)	6(6.6)	4(8.0)	7(12.7)
Source of water supply n(%)				
Home tap	13(5.8)	4(4.3)	6(12.0)	5(9.1)
Well or river	43 (19.3)	19(20.7)	9(18.0)	13(23.6)
Mixed	167 (74.9)	69(75.0)	35(70)	37(67.3)
Types of latrine n (%)				
Pit	170 (76.2)	73(78.5)	42(84.0)	42(76.4)
Flush	22 (9.9)	11(11.9)	7(14.0)	10(18.2)
No latrine	31 (13.9)	8(8.7)	1(2.0)	3(5.4)

Table 5. 2: Number of parasites infections, WHO stage and mean HIV-P24 of HIV/AIDS patients grouped according to CD4+-T cells categories attended at Tumbi Hospital and Chalinze Health Centre between April 2008 and March 2009

Number of parasite species per individual*				WHO Stage		HIV-1 P24
Zero	One	Two	Three or more	I/II	III/IV	Mean (SD)
97(43.5)	48(44.0)	17(28.8)	11(36.7)	100(54.4)	73(30.8)	5.4(20.9)
126(56.5)	61(56.0)	42(71.2)	19(63.3)	84(45.6)	164(69.2)	30.4(16.2)
223(100)	109(100)	59(100)	30(100)	184(100)	237(100)	15.3(20.3)

*Test for trend across ordered groups: Z = 1.69, p = 0.09

Table 5. 3: Univariate analysis of the association between parasites and clinical parameters before initiation of ART and other treatment of HIV and AIDS patients attended at Tumbi Hospital and Chalinze Health Centre between April 2008 and March 2009

	CD4+T cells count/µl		Haemoglobin g/dl		WHO clinical stage	
Infection status	**CD4<200 (%)**	**AOR* (95% CI)**	**HB<8.0 (%)**	**AOR* (95% CI)**	**III/IV (%)**	**AOR* (95% CI)**
No infection	126/223(56.5)	reference	42/223(18.8)	reference	121/223(54.3)	reference
Any parasites	122/198(61.1)	1.2(0.8-1.8)	64/198(32.5)	2.1(1.3-3.2)	116/198(58.6)	1.2(0.8-1.8)
Malaria only	27/50(54.0)	0.9(0.5-1.7)	12/50(24.0)	1.4(0.7-3.0)	25/50(50.0)	0.8(0.4-1.5)
Mixed helminths and Malaria	33/55(60.0)	1.2(0.6-2.1)	25/55(45.5)	3.8(1.9-7.1)	32/55(58.2)	1.2(0.7-2.2)
Helminths only	62/93(66.7)	1.6(0.9-2.6)	28/93(30.1)	1.9(1.1-3.3)	59/93(63.4)	1.5(0.9-2.5)
Hookworm	7/15(46.7)	0.6(0.6-1.8)	5/15(33.3)	2.1(0.9-6.7)	10/15(66.7)	1.6(0.5-4.8)
Schistosome	6/13(46.2)	0.7(0.2-2.2)	2/13(15.4)	0.9(0.2-4.5)	5/13(38.5)	0.6(0.2-1.8)
Strongyloides stercoralis	9/14(75.0)	1.5(0.5-4.5)	1/14(7.1)	0.4(0.1-2.9)	9/14(64.3)	1.5(0.5-4.7)
Ascaris lumbricoides	11/15(73.3)	2.2(0.8-7.2)	8/15(53.3)	5.3(1.8-15.7)	10/15(66.7)	1.7(0.6-5.2)

*Odds ratios adjusted to age and sex

Table 5. 4: Changes in CD4+Tcell counts between baseline and after six months of HIV/AIDS patients attended at Tumbi Hospital and Chalinze Health Centre between April 2008 and March 2009

ART status	With parasites at Baseline N=196				No parasites at Baseline N=222				New/re-infection
	Mean CD4 increase		Mean CD4 decrease		Mean CD4 increase		Mean CD4 decrease		
	N (%)	Mean(SD)	N (%)	Mean(SD)	N (%)	Mean(SD)	N (%)	Mean(SD)	
ART	129(85.4)	129.9(1.9)	19(42.2)	54.7(2.3)	125(85.0)	118.4(1.9)	23(30.7)	47.5(2.9)	16(88.9)
Not on ART	22(14.6)	60.2(2.8)	26(57.8)	181.4(2.1)	22(14.9)	66.7(2.5)	52(69.3)	157.8(2.9)	2(11.1)
Total	151(100)	111.6(2.2)	45(100)	109.3(2.7)	147(100)	108.6(2.1)	75(100)	109.2(3.4)	18(100)

Table 5. 5: Multivariable Logistic Regression for predictors of CD4+Tcell <200/µl after six months of follow-up of HIV and AIDS patients attended at Tumbi Hospital and Chalinze Health Centre between April 2009 and March 2009

Variables	Adjusted OR(95%CI)
Female	0.9(0.6-1.4)
Baseline CD4+Tcells counts*	2.4(1.3-4.7)
Baseline P24 Antigen levels	1.0(0.9-1.1)
Baseline WHO clinical stage**	1.0(0.7-1.6)
ART treatment	1.3(0.6-2.6)
Helminths or Malaria new/re-infection	1.6(0.4-5.7)

*Reference category CD4+T cells>200/µl.
** Reference category WHO clinical stage I/II.

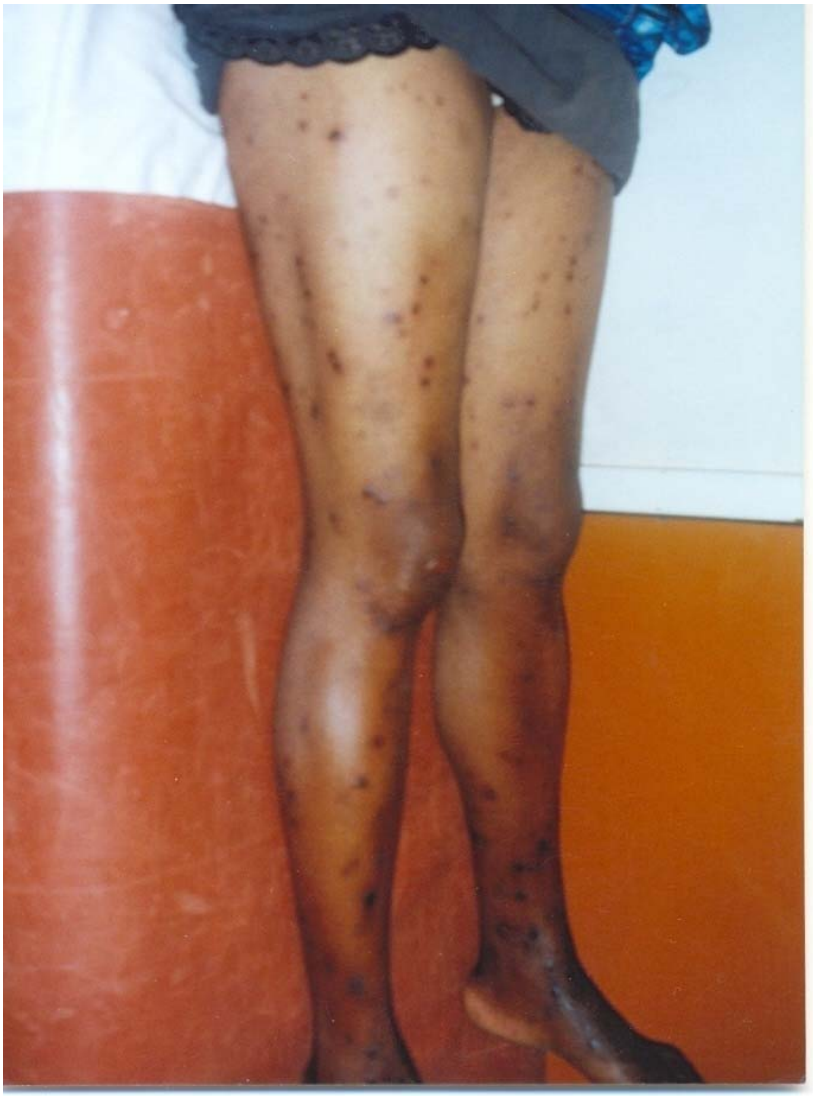

Figure 6 1: HIV/AIDS manifestations (Pruritic eczematous eruptions)

Chapter 6: HIV/AIDS clinical manifestations and their implication for patient clinical staging in resource limited settings in Tanzania

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Abstract

Background
Sub Sahara African HIV/AIDS management follows WHO clinical staging which requires CD4 counts as complement. Lacking CD4 counts facilities in rural health facilities remains a challenge. Simplified and sensitive clinical staging based on local clinical patterns is useful to ensure effective care without CD4 counts.

Objectives
To assess whether HIV local-based clinical manifestations can be used to guide HIV management in settings with limited access to CD4 counts in Tanzania.

Methods
A cross-sectional study conducted at Tumbi and Chalinze health facilities, Tanzania, documented clinical manifestations and CD4 counts in 360 HIV/AIDS patients. High frequency manifestations were used to predict level of immunosuppression with CD4 counts results as 'Gold standard'. Simplified management groups comprised of severe and moderate disease stages were formed based on clinical manifestations and CD4 counts.

Results
Weight loss (48.3%) and chronic cough (40.8%) were the most reported manifestation in the study population; followed by. Most symptoms were found to be highly specific (ranging from 56.4% of weight loss to 98.6% of the combination of cough, diarrhoea and difficult in breathing) with high positive predictive values (ranging from 56.8% of fatigue to 90% of the combination of cough, diarrhoea and difficult in breathing) in predicting severe immunosuppression. Chronic diarrhoea presented in 10.6% of patients, and predicted well severe immunosuppression either alone or in combination with other symptoms (with high likelihood ratios ranging from 1.83 to 3.27 at 95%CI). Headache, skin and fungal diseases presented highly but relatively weak in predicting

immunosuppression. Although, the combination of three symptoms predicted well WHO stages III/IV with high specificity and positive predictive values had low sensitivity. The sensitivity of all the presenting symptoms remained lower than 52%, and was not improved by including more signs and symptoms in the analysis.

Conclusions

HIV/AIDS clinics managing large cohorts should review and validate site specific HIV clinical manifestation in comparison with CD4 counts and WHO clinical stages. Based on local experiences simplified guidelines are useful for resource constrained settings without CD4 counting facilities.

Introduction

In sub-Saharan Africa, the transmission of Human Immunodeficiency Virus (HIV-1) occurs mostly through heterosexual contact and the progression to Acquired Immunodeficiency Syndrome (AIDS) and premature death is the reality for people in most poor areas with limited access to Antiretroviral Therapy (ART) [1, 2,3]. HIV disease progresses from an asymptomatic period of variable duration, through mild symptoms, to severe disease characteristic of cellular immunodeficiency [1].

Human Immunodeficiency Virus clinical presentation is known to be complex since AIDS was described in 1981[2, 3]. HIV can manifest in a variety of ways depending on the organs affected and concurrent infections prevalent in the area. The initial clinical presentation may mimic symptoms of common endemic diseases in that particular region [4, 5] However, the severity of manifestation depends on the infected individual's baseline health status. The most significant early manifestation of HIV infection in Africa was marked by slim disease (diarrhoea and wasting); tuberculosis; variety of Opportunistic Infections (OI); weight loss, fever; and dermatological symptoms[2,5,6]. With the exception of tuberculosis which continues to increase, other AIDS related diseases are declining gradually due to the widespread use of OI drugs.

World Health Organization (WHO) has established a four stage clinical classification system determined by the presence of Opportunistic Infections and other HIV related conditions [7]. This classification tried to incorporate most of the AIDS-defining illnesses occurring in all regions of the world making a global tool for HIV/AIDS patients care and treatment. It has been a very useful tool in Sub Saharan Africa at the introduction of antiretroviral drugs and establishment of HIV/AIDS treatment cohorts [8]. It helped to capture rapid deteriorating patients and

initiation of ART in settings with limited diagnostic resources and less trained clinicians.

Antiretroviral drugs are widely available nowadays and continue to be scaled up in remote rural areas of sub Saharan Africa [9, 10]. The aim of rapid scale up is to reach more people living with HIV and AIDS who cannot easily access ART services in urban hospitals. The main challenges to this plausible strategy include availability of qualified health workers and laboratory services to ensure quality care and the monitoring of drug use [11-13]. In addition, most patients including HIV-infected patients in Sub Saharan Africa present late for hospital care and treatment when the disease has advanced [13-15]. By then initial AIDS signs and symptoms might have been treated empirically through self medication or use of herbal medicines. Such remedial actions usually obscure important AIDS clinical features and make it difficult for the attending clinician to solicit signs and symptoms to properly stage the patient.

It is evident that HIV/AIDS patients' management in Sub Saharan Africa continues to be guided primarily by clinical staging [8, 16, 17] owing to the insufficient availability and/or frequent breakdowns of CD4 cells count machines, shortage of qualified medical personnel and laboratory reagents and other logistic issues and challenges [18]. On the other hand WHO clinical staging depends on a patient presenting signs and symptoms; knowledge and skills of the health care worker to make a definitive staging [8,17,19]. Furthermore, WHO clinical staging is less sensitive in identifying patients with CD4 cell counts between 200 -350 cells per µL [4, 20]. Therefore, it fails to identify some patients in need of ART.

Taking into considerations the complexities of HIV clinical manifestation in our setting which often does not match WHO clinical staging. Clinicians in lower health facilities, who are expected to attend to HIV patients in their local settings, need

simplified and easy to use clinical staging guidelines developed by utilizing site specific data and clinical experiences. This approach could effectively support management of HIV/AIDS patients in ART cohorts based on site specific experiences. Moreover, the broader availability of ART as well as new approaches to deal with opportunistic infections call for a review of the clinical presentations seen within care and treatment programs in different settings. To date, no studies have proposed simplified HIV/AIDS clinical staging based on local experience. With the inspiration of WHO validated HIV/AIDS clinical definition, our study aimed at developing simplified HIV/AIDS clinical staging system based on data generated locally from peri-urban and rural health facilities to allow more effective patient management and ART cohorts at peripheral level in the absence of CD4 counts.

Methods

Setting and study participants

The study was conducted at Tumbi Regional Hospital and Chalinze Health Centre in Pwani Region, Eastern Tanzania between April and December 2008. Tumbi Regional Hospital is located 40 km from Dar es Salaam, the commercial capital of Tanzania. The hospital has a bed capacity of 200 beds and serves as a regional referral Hospital. Chalinze Health Centre is located 70 km from Tumbi Hospital at the junction of the main upcountry highways with HIV prevalence of 15%. The Pwani Region HIV prevalence is 7%. Both facilities provide services to a mixture of patients from urban and rural villages. Most residents of Chalinze reside in rural villages and generate income from farming and trading of different types of goods.

Tumbi Hospital runs two separate HIV/AIDS clinics for adults and children since 2007. At the time of initiation of this study in April 2008, Tumbi Hospital had enrolled a total of 3851 patients

to care and treatment. And Chalinze Health Centre had enrolled a total of 450 patients to care and treatment.

The inclusion criteria for our study population included those aged 15 and above years; permanent residence to the health facility catchments area; and first time enrolment to care and treatment services; no prior use of ARVs and or co-trimoxazole prophylaxis.

A total of 360 female and male patients consented to participate in the study. Recruitment of study participants lasted for 3 months. The current recommended ARV combination regimen for adults and adolescent include:
AZT + 3TC+NVP or EFV,
D4T+3TC+NVP/EFV
TDF+FTC+NVP/EFV
TDF+3TC+NVP/EFV

Data collection
Each consenting patient was clinically examined in the standard way that involved a detailed history, physical examination and laboratory tests. Additional laboratory tests depended on the suspected diagnosis. Patients' socio-demographic characteristics and clinical information were recorded in a structured report form in addition to routine patient case report forms.

Laboratory procedures
Blood, sputum, urine and stool samples were collected and analyzed. Blood samples were analyzed for CD4 cell counts, HIV-1 P24 plasma ELISA assay, haemoglobin, liver and renal function tests. Blood was collected in EDTA tubes for enumeration of CD4 cells by using FACS count (BD Biosciences, California, USA). Biochemistry and haematological parameters were analyzed using Biochemical analyzer (Italy) and haematological analyzer (Pentra 80, France) respectively. Thick blood smears were Giemsa stained and microscopically examined for Malaria parasitaemia [21]. Sputum specimens were stained using Ziehl-

Neelsen technique and examined for mycobacterium tuberculosis [22].

Stool samples were fixed using sodium acetate-acetic acid-formalin (SAF) solution and microscopically examined for intestinal parasites. Part of freshly passed stool was inoculated and cultured in Xylose Lysine Deoxycholate Agar (XLD) media for Salmonella and Shigella species. A direct microscopic examination was performed on urine samples. This paper focuses on CD4 cell counts results in comparison to the WHO clinical staging.

Data analysis

All data was entered into Microsoft ®Access, and analyzed using Stata Intercooled version 9.

Each clinical symptom or sign was coded and counted individually to estimate the frequency of occurrences from every patient. About 140 different signs and symptoms were recorded. The frequencies were then used to estimate the proportion of patients with that particular sign or symptom.

Using CD4 count results and a cutoff point of 350 cells/µL patients were categorized into two management groups of severe immunosuppression (CD4+ T-lymphocytes counts below 350 cells per µL) and moderate immunosuppression (CD4+ T-lymphocytes counts above 350 cells per µL). In addition, presented signs and symptoms were used to perform WHO staging. Based on clinical manifestations of the study patients, we determined the probability of each symptom/sign alone or in combination of up to three to predict severe immunosuppression and WHO clinical stages III/IV. The probability were determined in terms of sensitivity, specificity, predictive values and likelihood ratio using CD4 cells count level as the “gold standard”. Only

symptoms which had high frequency and troubled the patient for more than two weeks were used.

Ethical approval

The study received scientific and ethical approval from the Muhimbili University of Health and Allied Sciences Research Ethics Review Board (Ref.No.MU/RP/AEC/Vol.XII/58). Permission was granted by Region, District and hospital authorities. Verbal informed consent for participation was obtained from patients using local Kiswahili language.

Results

Socio-demographic and clinical characteristics

In total, 360 HIV-infected patients consented to participate in the study and 331(91.9%) patients provided complete data for analysis. Majority of the patients resided in rural areas 223(67.4%), the others were from semi-urban areas. The median CD4+ T-lymphocytes counts was 84(IQR 29-127) and 380(IQR 279-536) respectively. There were 191(57.7%) patients with severe immunosuppression comprising of 68(35.6%) males and 123(64.4%) females. The median age was comparable in both groups of patients with severe or moderate immunosuppression. Patients classified with WHO clinical stage III/IV, 60(42.9%) had moderate immunosuppression and 54(28.3%) of those with WHO clinical stage I/II had severe immunosuppression.

Patient's main presenting symptoms and signs at recruitment

Frequencies of the most recorded symptoms and signs are shown in Table 6 2. We report symptoms and signs that persisted for more than two weeks. Weight loss of more than 5 kg was the most frequent 160(48.3%), followed by chronic cough

135(40.8%). Diarrhoea was less common 35(10.6%) in this study population. Recurrent fever was recorded in 132(39.8%) of the patients; other symptoms with high frequency included headache 105(31.7%); Peripheral neuropathy 57(17.2%) and fatigue 88(26.6%). patients had various types of skin diseases, but Pruritic Papular Eruptions was the most common dermatological condition. Thirty six (11%) patients presented with genital discharge; 12(33%) of them had sexually transmitted infections. In addition to major clinical symptoms and signs; 132 (37%) patients presented with mild non-specific various clinical features. Major AIDS-defining Opportunistic Infections diagnosed in this study included: Tuberculosis (15%); *Pneumocystis carinii* Pneumonia (7%); Herpes zoster (5%); Cryptococcus Meningitis (3%); and Kaposi's sarcoma (3%).

Performance of clinical features to predict severe immunosuppression

In Table 6 2, Table 6 3 and Table 6 4 the performance of each AIDS presenting symptom alone or in combination with other symptoms in predicting severe immunosuppression is demonstrated. The sensitivities of single main complain were below 50% except for weight loss of more than 5% and headache which was 51.8%. However, the specificity of most symptoms was high with fungal infection and chronic diarrhoea presenting the highest specificities of 93.6% and 92.9% respectively. Sensitivity declined with higher combination of major symptoms per patient (Table 6 3 and Table 6 4). However, the Positive Predictive values (probability of correct diagnosis) for severe immunosuppression increased with higher combination.

Patients presenting with chronic diarrhoea had about two times more likely to have severe immunosuppression (Likelihood ratio 1.83, 95%CI 0.91 to 3.69). Diarrhoea is an important predictor of severe immunosuppression even when presenting in

combination with other major symptoms (Likelihood ratio ranging from 1.78 to 4.03, for two and three combination of symptoms).

Most of the symptoms documented as single or in combination with other symptoms had likelihood ratio of greater than one indicating their association with severe immunosuppression. Whereas the likelihood ratio of headache (0.98, 95%CI 0.71-1.34), fatigue (0.96, 95%CI 0.67-1.38); and the combination of abdominal pain and fatigue (0.87, 95%CI 0.51-1.49) were less than one indicating lack of association with severe immunosuppression.

Since most of the symptoms recorded are not part of the list of clinical conditions used to determine WHO clinical staging, we determined the diagnostic properties of combination of three signs and or symptoms. The results in Table 6 5 show an attempt to use combination of three symptoms to allocate patients into WHO clinical stages III/IV. The sensitivities ranged from 4.6%(combination of cough, diarrhoea and difficult in breathing) to 37.3% (combination of cough, fever, weight loss) however the predictive values were above 80%, indicating the high probability of correct allocation of patients to WHO stages III/IV if presented with multiple combination of major signs and symptoms. The likelihood ratios were greater than 2 in all the three combinations indicating that it is useful to use these combinations to clinically classify patients into WHO stages III/IV.

Discussion

This study attempted to explore the extent to which HIV/AIDS presenting symptoms at a given location could be used to screen patients with severe immunosuppression and eventually decide appropriate model of care for HIV-infected patients in settings with limited access to CD4 counts. Since the number of HIV/AIDS patients with unusual clinical presentations continues to increase due to viral mutations, self medications with Opportunistic Infection drugs and use of local herbs practices

which mask the known classical HIV/AIDS manifestations. Review of clinical manifestations and development of validated HIV-clinical staging that maximize both sensitivity and specificity tailored to a particular geographical and endemic area in comparison to the well established WHO-staging should be encouraged.

The clinical profiles of about 34% of the study patients were unique and obscured not fitting with WHO clinical criteria, which in turn resulted in WHO staging that was inconsistent with their CD4 cell counts. The majority of the patients presented with clinical features of weight loss (and wasting); chronic cough; and persistent fever for more than 2 weeks. These are common symptoms and signs which were described as early HIV manifestation and were significantly associated with sero-conversion in the first decades of HIV epidemic [23, 24] and were among the bases of WHO staging together with presence of opportunistic infection. We also, observed a marked shift in AIDS clinical manifestation from the classical AIDS clinical manifestations [23] which previously was marked by profound weight loss of more than 10% body weight; chronic diarrhoea and prolonged fever to a mixed picture of signs and symptoms [23-25]. Although, our patients had reported weight loss, the weight loss was limited to more than 5 kg and less than 5% (data not shown) of their initial body weight. The clinical spectrum seen among the patients in both study sites are quite representative to the current overall clinical pictures of the HIV/AIDS patients in the area. The two sites are the only care and treatment centres in the whole area.

Interestingly, only 10.6% of the patients presented with chronic diarrhoea which indicates a marked reduction in occurrence of diarrhoea among HIV/AIDS patients. Diarrhoea was well known to affect between 40% and 80% of HIV infected persons and was also associated with high mortality rates in Sub-Saharan Africa [24, 26, 27]. The reduction in prevalence of diarrhoea in

HIV infected people can be explained by the now broader availability of OIs drugs and co-trimoxazole without prescription. Working at care and treatment centres, we recruited newly diagnosed HIV patients that were all included in the ART cohorts according to the national control programme. We expected to record more pre-AIDS signs and symptoms such as generalized lymphadenopathy, Herpes zoster and mucocutaneous lesions. Instead, one third of our patients presented with minor non-specific and often no symptoms. While, at the same time about one third of the patients had CD4 cell counts less than 350 cells per µL. Herpes zoster was diagnosed in 5% of patients, most of them had CD4 cell counts below 200 cells per µL which is contrary to the common believe that Herpes zoster is a stage II disease. It is a reality in most rural, poor communities to accept a HIV test after suffering for a long time and tried on all kinds of remedies without success. During this time their CD4 cell counts progressively declined.

Most of the known common HIV related opportunistic infections were less frequent than expected in this population despite many patients having CD4 cell counts less than 350 cells per µL. It is well established that patients at this level of CD4 cell counts have high risk of AIDS opportunistic infections and AIDS related cancers [28]. Tuberculosis was diagnosed in only 15% of the patients despite the high frequency of chronic cough and difficulty in breathing. Patients with extra pulmonary tuberculosis and *Pneumocystis carinii* pneumonia could be missed due to limited respective diagnostic facilities. The diagnosis of these diseases was based on sputum and chest x-ray findings. In routine practice, tuberculosis in HIV-infected patients requires regular screening at every visit because single screening does not exclude latent infection that can flare up in the course of HIV disease progression.

Cryptococcus meningitis and Kaposi's sarcoma were diagnosed in only 3% of the patients. However, the lower rate of HIV related

cancers can be due to the small sample size of this study. Overall, the different clinical patterns and frequencies of opportunistic infections may largely be due to changed approaches in the clinical management brought forward by (i) the broader availability of ART in combination with the establishment of care and treatment centres as part of the national control program and (ii) the new approaches to handle prophylactically and therapeutically opportunistic infections also outside the national HIV/AIDS control program.

Patients with moderate immunosuppression are symptomatically expected to fit in WHO stages I/II whilst those with severe disease to be stages III/IV and vise versa. However, according to their CD4 cell counts, 29% and 49% of patients in clinical stages I and II were supposed to be in WHO clinical stages III or IV respectively. Similarly, 37% and 25% of patients in WHO clinical stages III and IV respectively, were supposed to be in WHO clinical stages I or II respectively. The level of incorrect classification found in this study is almost similar to Ugandan experiences where about 50% of patients were inappropriately staged [20]. In routine clinical practice WHO clinical stages determine the direction of case management. Patients in clinical stages I and II usually receive long time appointments accompanied by minimum laboratory investigations. While, patients in clinical stages III and IV usually receive clinical and laboratory assessment to determine their eligibility to start ART. Therefore, when a sizable proportion of patients cannot be staged correctly at first contact in ART clinics, the initiation of ART is delayed and higher mortality rates can be expected in the first three months of ART [13].

More than half of our patients were in WHO clinical stages III and IV which was consistent to the number of patients with CD4 cell counts of less than 350 cells per µL. This is the reality of late presentation and a challenge to ART programs. Using the cut off point for severe immunosuppression of CD4 cell counts <350

cells per µL, comparison is more conservative based on the Tanzania Care and Treatment Guidelines [16]. Taking into consideration the high proportion of patients presenting late with obscured clinical features to care and treatment for the first time, it appears advantageous to classify patients based on local understanding of HIV-disease manifestations and to have at least one CD4 count measurement before initiation of ART. Such an approach simplifies the process of clinical management and reduces the chances of missing appropriate staging and hence avoid delays in starting ART can be avoided.

In our study, skin diseases and fungal infections of the skin and mucous membranes indicated severe immunosuppression with a low sensitivity (10.9% and 7.9% respectively). Similarly, these symptoms were weak predictors of severe immunodeficiency based on CD4 decline. Although these symptoms are frequently diagnosed cannot be used to categorize level of immunosuppression. Most of the symptoms showed low sensitivity in predicting severe immunosuppression and a high risk of false negative results, thus many patients with CD4<350 can be missed if these symptoms are used in routine clinical management. However, these symptoms were highly specific and high positive predictive values which increased with the number of symptom combinations for severe immunosuppression. Therefore the presence of combination of HIV-specific clinical symptoms in a patient can be used to initiate ART.

Based on these study findings, exclusive use of WHO clinical staging of HIV/AIDS patients to decide appropriate model of care, remains a challenge for clinicians working in settings with limited access to CD4 counts. The absence of clinical illness in fitting with WHO clinical stages cannot be used to rule out the need for ART. We then recommend use of HIV-specific symptoms based on local experiences to classify HIV-infected patients into severe and moderate immunosuppression based on duration of clinical

manifestations. This classification guided by local clinical experience - requires further validation. But for patients with unusual HIV-disease presentation estimation of CD4 counts is still needed to decide model of care. We recognize the small sample size used in this study as a limitation. However the composition of patients from rural and urban settings implies that the guidelines established can be used at a regional level. Therefore and besides our current own efforts, more studies should be conducted to validate the proposed approach of staging, not only for patients' classification but also for monitoring drug side effects and treatment failure in other geographical and endemic settings.

Conclusion

The broader availability of HIV/AIDS treatment as well as new approaches to deal with opportunistic infections, we call for a review of the clinical presentations seen within care and treatment programs in different settings. Besides applying the WHO clinical staging care and treatment centres that look after large cohorts of HIV and AIDS patients information should also develop and validate site specific guidelines based on local clinical experiences.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BI Participated in conception and design of the study. He also coordinated all activities pertaining to collection and management of data, analysis and interpretation of data. He has been involved in drafting the manuscript and revising it.

MT has been involved in conception and design of the study; drafting the manuscript and revising it critically and has given the final approval of the version to be published.

OM has been involved in drafting the manuscript and revising it critically.

SFR has been involved in data analysis and drafting the manuscript.

FM has been involved in conception and design of the study; drafting the manuscript.

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References:

[1] Fauci AS, Pantaleo G, Stanley S, Weissman D. (1996). Immunopathogenic Mechanisms of HIV infection. Ann. Internal Medicine.124:654-663.

[2] Piot P Colebunders R. (1987). Clinical manifestations and Natural History of HIV infection in Adults; Western J med.147: 709-712.

[3] Idrisa M. (2005) Chapter 6. The pathophysiology and clinical Manifestations of HIV/AIDS. In Abdulsalami N *et al*. AIDS in Nigeria. Available online from: Harvard University Press: www.hup.harvard.edu/catalog/ADEAID.html.

[4] Strecker W, Gurtler L, Schilling M,Binibangili M, Strecker K. (1994), Epidemiology and clinical manifestation of HIV infection in northern Zaire. Eur J Epidemiol. 10(1): p. 95-8.

[5] HolmesCB, Losina E, Walensky R P, Yazdanpanah Y, Freedberg K A (2003). Review of human immunodeficiency virus type 1-related opportunistic infections in sub-Saharan Africa. Clin Infect Dis. 36(5): 652-62.

[6] Grant A. (2002). Clinical features of HIV disease in developing countries; Leprosy Review. 73(2): 197-205

[7] World Health Organization (2006). Antiretroviral Therapy for HIV infection in Adults and adolescents in resource-limited settings: towards universal access recommendation for public health approach 2006 revision

[8] World Health Organization (2005). Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for Surveillance: Africa Region 2005.

[9] Stringer JS, ZuluI, Levy J. Levy J, Stringer EM, Mwango A, Chi BH, Mtonga V, Reid S, Cantrell RA, Bulterys M, Saag MS, Marlink RG, Mwinga A, Ellerbrock TV, Sinkala, M (2006). Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. JAMA. 296(7): p. 782-93.

[10] Chien CV. (2007). HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare? PLoS ONE 2(3): e278.

[11] Mullan F, Frehywot S. (2007). Non-physician clinicians in 47 sub-Saharan African countries. Lancet. 370(9605): p. 2158-63.

[12] Morris MB, Chapula BT, Chi BH, Mwango A, Chi HF, Mwanza J, Manda H, Bolton C, Pankratz DS, Stringer JS, Reid SE. (2009) Use of task-shifting to rapidly scale-up HIV treatment services: experiences from Lusaka, Zambia. BMC Health Serv Res. Jan 9;9: 5.

[13] World Health Organisation: (2007) Towards Universal Access: Scaling up priority HIV/AIDS in the health sector. Progress report. 2007.

[14] Isidore S, Mohamadou S, Scho¨nenberger AM, Menten J and Boelaert M (2009). Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North Province, Cameroon Tropical Medicine and International Health. 14(1):p 36–43 January 2009

[15] Dale M N, Bowmanb D, Susan D, Foster, Godfrey-Faussett P. (2004) .Patient care seeking barriers and tuberculosis programme reform: a qualitative study Health Policy 67:93–106

[16] Ministry of Health Tanzania (2008). National AIDS control programme-National Guidelines for the management of HIV and AIDS 3rd edition, 2008

[17] Spacek LA, Gray RH, Wawer MJ, Sewankambo NK, Serwadda D, Wabwire-Mangen F, Kiwanuka N, Kigozi G, Nalugoda F, Quinn TC (2006). Clinical illness as a marker for

initiation of HIV antiretroviral therapy in a rural setting, Rakai, Uganda. Int J STD AIDS. **17**(2)**:**116-120.

[18] Willoughby VR, Sahr, F, Russell, JB, Gbakima, AA (2001). The usefulness of defined clinical features in the diagnosis of HIV/AIDS infection in Sierra Leone. Cell Mol Biol (Noisy-le-grand),. 47(7): p. 1163-7.

[19] Zachariah R, Ford N, Philips M, Lynch S, Massaquoi M, Janssens V, Harries AD (2008). Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. Trans R Soc Trop Med Hyg,

[20] Shabbar J, Birungi J, Grosskurth H, Amuron B, Namara G, Nabiryo C,Coutinho A.(2008). Use of WHO clinical stage for assessing patient eligibility to antiretroviral therapy in a routine health service setting in Jinja, Uganda: AIDS Research and Therapy. 5:4

[21] NCCLS, 2000. Laboratory Diagnosis of Blood-Borne Parasitic Diseases. Approved Guideline M15-A. National Committee for Clinical Laboratory Standards, Villanova, PA.

[22] Lennette EH, Balows A, Hausler Jr W.J, Shadomy HJ, eds. 1985. Manual of Clinical Microbiology. 4th ed. American Society for Microbiology, Washington, D.C;1985.

[23] World Health Organization AIDS surveillance case definition, Bangui October 1985, at a conference of public health officials including representatives of the Centres for Disease Control (CDC) and World Health Organization (WHO) in, Bangui Central African Republic.

[24] Serwadda D, Mugerwa RD, Sewankambo NK, Lwegaba A, Carswell JW, Kirya GB, Bayley AC, Downing RG, Tedder RS, Clayden SA. (1985). Slim disease: a new disease in

Uganda and its association with HTLV-III infection. Lancet,. 2(8460): p. 849-52.

[25] Carswell JW (1988). Clinical manifestations of AIDS in tropical countries Trop Doct. Oct; 18(4):147-50.

[26] Morgan D, Ross A, Mayanja B, Malamba S, Whitworth J (1998). Early manifestations (pre-AIDS) of HIV-1 infection in Uganda. AIDS. 12(6): p. 591-6.

[27] Lesbordes, JL, McCormick JB, Beuzit Y, Ramiara JP, Vohito DM, Meunier DM, Georges MC, Gonzalez JP, Georges AJ (1985).Clinical aspects of AIDS in the Central African Republic. Med Trop (Mars). 45(4): p. 405-11.

[28] Deuffic-Burban S, Losina E, Wang B, Gabillard D, Messou E, Divi N, Freedberg KA, Anglaret X, Yazdanpanah Y (2007). Estimates of opportunistic infection incidence or death within specific CD4 strata in HIV-infected patients in Abidjan, Cote d'Ivoire: impact of alternative methods of CD4 count modelling. Eur J Epidemiol. 22(10): p. 737-44.

Table 6.1: Characteristics of patients at first clinical assessment grouped by CD4 cell count

Variable	All patients (N=331)	CD4>350 cells per µL (N=140)	CD4=350 cells per µL (N=191)
Median age in years(IQR)	36(12)	36 (30-44)	36 (32-42)
Male		49 (35.0%)	68 (35.6%)
Female	117(35.3)	91 (65.0%)	123 (64.4%)
	214(64.7)		
Residential status			
Semi-urban	108(32.6)	47 (33.6%)	61 (31.9%)
Rural	223(67.4)	93 (66.4%)	130 (68.1%)
WHO Clinical stage			
I	59(17.8)	42 (30.0%)	17 (8.9%)
II	75(22.7)	38 (27.1%)	37 (19.4%)
III	95(28.7)	35 (25.0%)	60 (31.4%)
IV	102(30.8)	25 (17.9%)	77 (40.3%)
Median CD4+ T- cells per µL (IQR)	158(253)	380 (279-536)	84 (29-127)

Table 6.2: Sensitivity, specificity, predictive values and likelihood ratio of a single symptom to predict CD4d”350 cells/µl

Symptom	Patients with the symptom n (%)	CD4=350 cells per µL				
		Sensitivity	Specificity	PPV	NPV	Likelihood ratio (95%CI)
Weight loss >5kg	160 (48.3)	51.8	56.4	61.8	46.2	1.19 (0.94-1.50)
Cough	135 (40.8)	44.5	64.3	62.9	45.9	1.37 (1.03-1.82)
Fever	132 (39.8)	45.0	67.1	65.1	47.2	1.25 (0.95-1.64)
Headache	105 (31.7)	51.8	56.4	61.8	46.2	0.98 (0.71-1.34)
Fatigue	88 (26.6)	26.2	72.8	56.8	41.9	0.96 (0.67-1.38)
Dizziness	70 (21.1)	24.1	82.8	65.7	44.4	1.40 (0.90-2.19)
Peripheral neuropathy	57 (17.2)	17.3	82.9	57.9	42.3	1.01 (0.62-1.63)
Diarrhoea	35 (10.6)	13.0	92.9	71.4	43.9	1.83 (0.91-3.69)
Skin diseases	34 (10.3)	10.9	90.7	61.8	42.8	1.18 (0.61-2.28)
Fungal infection (skin and mucous membranes)	24 (7.3)	7.9	93.6	62.5	42.7	1.22 (0.55-2.71)

Table 6. 3: Sensitivity, specificity, predictive values and likelihood ratio of two symptoms to predict CD4d”350 cells/µl

Symptom	Patients with the symptom n (%)	CD4=350 cells per µL				
		Sensitivity	Specificity	PPV	NPV	Likelihood ratio (95%CI)
Weight loss and fever	96 (29.0%)	31.9	75.0	63.5	44.7	1.27 (0.89-1.82)
Weight loss and cough	87 (26.3%)	30.9	80.0	67.8	45.9	1.54 (1.04-2.28)
Cough and fever	74 (22.4%)	26.2	82.9	67.6	45.1	1.53 (0.98-2.36)
Abdominal pain and fatigue	46 (13.9)	15.2	88.1	65.2	41.4	0.87 (0.51-1.49)
Peripheral neuropathy and headache	34 (10.3)	10.9	90.7	61.8	42.8	1.18 (0.61-2.28)
Fever and diarrhoea	24 (7.2%)	9.4	95.7	75.0	43.6	2.19 (0.89-5.39)
Weight loss and diarrhoea	24 (7.2%)	8.9	95.0	70.8	43.3	1.78 (0.76-4.18)
Cough and Diarrhoea	18 (5.4%)	6.8	96.4	72.2	43.1	1.91 (0.69-5.22)

Table 6. 4: Sensitivity, specificity, predictive values and likelihood ratio of three symptoms to predict CD4d”350 cells/µl

Symptom	Patients with the symptom n (%)	CD4=350 cells per µL				
		Sensitivity	Specificity	PPV	NPV	Likelihood ratio (95%CI)
Cough, fever, Weight loss>5kg	61(18.4%)	21.9	86.4	68.9	44.8	1.62 (0.98-2.66)
Weight loss>5kg Difficult breathing poor appetite	38(14.5%)	13.6	91.4	68.4	43.7	1.58 (0.83-3.04)
Headache, Difficult breathing, poor appetite	21(6.34%)	7.9	95.7	71.4	43.2	1.83 (0.726-4.60)
Fever, headache, diarrhoea	13(3.9%)	5.7	98.6	84.6	43.4	4.03 (0.91-17.90)
Abdominal pain headache diarrhoea	13(3.9%)	5.2	97.8	76.9	43.1	2.44 (0.68-8.71)
Fever, diarrhoea, Difficult breathing	12(3.6%)	4.7	97.8	75.0	42.9	3.27 (0.72-14.92)
Cough, diarrhoea difficult breathing	10 (3.0%)	4.2	98.6	80.0	42.9	2.93 (0.63-13.59)

Table 6. 5: Sensitivity, specificity, predictive values and likelihood ratio of three symptoms to predict WHO clinical stages III and IV in HIV infected persons

Symptom/sign	Frequency of signs and symptoms (%)	WHO clinical stage III /IV				
		Sensitivity	Specificity	PPV	NPV	Likelihood ratio (95%CI)
Cough, fever, Weight loss>5kg	61(18.4%)	37.3	62.4	81.9	45.6	3.09 (1.67-5.71)
Weight loss>5kg Difficult breathing poor appetite	38(14.5%)	16.8	96.3	86.8	44.0	4.49 (1.79-11.20)
Headache, Difficult breathing, poor appetite	21(6.34%)	8.6	97.0	80.9	41.9	2.89 (0.99-8.40)
Fever, headache, diarrhoea	13(3.9%)	5.6	98.5	84.6	41.5	3.74 (0.84-16.61)
Fever, diarrhoea, Difficult breathing	12(3.6%)	5.1	98.5	83.3	41.4	3.40 (0.76-15.27)
Cough, diarrhoea difficult breathing	10 (3.0%)	4.6	99.3	90.0	41.4	6.12 (0.79-47.75)

Figure 7.1: A nurse conducting ART adherence counselling to a patient and treatment supporter

Chapter 7: A case-control study of factors associated with non-adherence to antiretroviral therapy in rural HIV and AIDS care and treatment clinics of Tanzania

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Abstract

Background

Consideration of adherence to combination antiretroviral therapy (ART) among patients in resource limited settings is important in expanding access to ART. Non-adherence is one of the major causes of treatment failure which leads to increased morbidity and mortality caused by Opportunistic Infections. Optimal ART adherence is essential for maximal suppression of viral replication and long term survival of patients. In order to develop effective public health interventions in the context of scaling ART services to rural areas, it is important to evaluate factors associated with non-adherence among HIV-infected individuals in rural areas. The purpose of this study was to identify factors related to non-adherence in rural and semi-urban settings of Tanzania.

Methods

A case-control study was carried out at Tumbi Hospital and Chalinze Health centre. A structured questionnaire was used to assess adherence to doses instruction and time schedule. Patients with less than 95% adherence were defined as cases while those with more than 95% adherence became controls. A structured questionnaire containing factors known to be associated with non-adherence to ART in similar settings was administered. Univariate and multivariate conditional logistic regression was performed to identify factors associated with non-adherence.

Results

A total of 79 cases and 237 controls matched by age and sex were studied. A high proportion of cases and controls (77.2% and 84.8%) had good knowledge of ART benefits, adherence and eligibility. Majority of cases (73.3%) and controls (69.2%) used public transport to access ART services. More than half of cases (53.2%) missed clinic appointments due to lack of fare or

other reasons and was associated with ART non adherence (mOR 4.2, 95%CI, 2.2-8.1 and 2.1,95%CI 1.2-4.2). Disclosure to confidants only and failure to disclose HIV-test positive status were associated with non adherence (mOR 3.3, 95%CI 1.3-8.5 and 2.3, 95%CI 1.2-7.1). Alcohol use was associated (mOR 1.9, 95%CI 1.4-3.7) with non adherence to ART. Patients who were not satisfied with providers were more likely to be non adherence to ART (mOR 2.0, 95%CI 1.2-3.8).

Conclusions
These findings show that adherence is a dynamic process that varies depending on region or cohort specific adherence factors. Adherence improvement strategies need to consider site specific adherence determinants, patient experiences and concerns.

Background

Tanzania like many other sub-Saharan countries with an estimated 2 million persons living with HIV and AIDS has the greatest burden of disease [1], [2]. The prevalence is estimated at 5.7% in the population segment aged 15-49 years old with women being highly affected than men [3]. The epidemic shows regional variations and urban residents have considerably higher infection levels at 10.9% compared with rural residents 5.2% [4].

Tanzania benefited from the Global fund for HIV/AIDS, Malaria and Tuberculosis fund; SDC fund coupled with the U.S.A Presidential Emergence Fund for AIDS which were made available in 2004. The National response to HIV and AIDS added care and treatment in the prevention interventions package [5].

The Government of Tanzania introduced the HIV and AIDS care and treatment program with the aim of prolonging the lives of PLHA, to restore their mental and physical functions and to improve quality of life [1]. Through the National AIDS Control

Program, the MOH Tanzania adopted a stepwise approach to scale up antiretroviral therapy (ART) services in the country. A pilot HIV/AIDS care and Treatment clinic was started in late 2004 at Muhimbili National Hospital, which was then followed by establishment of similar clinics in zonal and regional hospitals. A model integrated care and treatment HIV-clinic was established at Ifakara Hospital in April 2005 to document experiences and challenges of providing ART in rural settings through applied research [6]. This careful rather cautious approach was aimed at establishing capacity to provide training and supervision roles to the lower facilities. However, due to increased demand for Antiretroviral therapy in all parts of the country a quick rapid scale up strategy was implemented with support from Non-Government Organizations (NGO). HIV and AIDS care and treatment clinics were established in selected rural health centres with large volume of patients.

ART has substantially decreased morbidity and mortality rates for those with HIV-infection in developed and developing countries like Tanzania [7]. The use of simpler ARV fixed dose combination regimens have overcome the prescription complexities. Thus, lower level health providers can prescribe ARVs after short term training.

Concerns about poor adherence to combination antiretroviral drugs (ARV) among patients living in resource limited settings have been an important consideration in expanding the access to ART [8]. Mainly due to possibility of poor adherence to treatment because of inadequate resources and ARV prescription requirements that the drugs are taken on time, every time and side effects are managed accordingly [9]. Poor adherence to ART is one of the major causes of treatment failure which leads to increases in morbidity and mortality caused by infection with opportunistic diseases [10], [11]. Good adherence to ART is essential for maximal suppression of viral replication, avoidance of resistance and long term survival of patients [12], [13], [2],

[14]. A minimum of 95% compliance is needed to achieve the desired virologic outcomes [15], [12].

Many studies have examined adherence to ART in resource limited settings with varied results due to differences in socio-cultural and socio-economical contexts of the populations being studied [16]. Several factors have been found to be associated with sub optimal adherence to treatment. Medication factors such as dosing frequencies and higher daily pill numbers were highly associated with poor adherence especially before the development of fixed dose combination [15]. Fixed dose ARVs combinations (FDC) have reduced the number of pills and the frequency of intake is reduced to twice daily. In most resource limited settings commonly use Nevirapine-based HAART with 1 of 2 backbone nucleoside combinations of Stavudine/Lamivudine or Zidovudine/Lamivudine. Nevirapine-based HAART delivered as FDC is convenient to take, easy to adhere to, potent, well tolerated, and reserves future treatment options in case of drug failure [17].

Adverse drug side effects, lower level of patient education and little experience with HIV/AIDS symptoms are strongly associated with non adherence to treatment in some settings [18], [19]. Understanding of adverse drug side effects can be a challenge in setting with limited laboratory diagnosis, presence of infection with similar clinical manifestation and low level of education like most of the rural areas in sub Saharan Africa.

Good adherence to ART has been shown in sub Saharan Africa [20], [21], though cannot be generalized to all settings. In some rural areas where food is scarce and patients have to travel long distances to seek care, adherence to dietary instructions and time intervals between doses can result into sub optimal adherence to ART [22] [23].

Among the psychosocial attributes related to non adherence to ART include lack of social support, depression, active substance

abuse and alcohol use, stigma and fear of disclosure of HIV sero status [24], [25], [26].

A rapid increase in HIV-1 prevalence and testing awareness among people living in rural and semi-urban communities has been seen in Tanzania [27]. Rural populations have limited health care and social service resources. They typically report difficulties in accessing appropriate health care including HIV care and treatment services. Rural communities are classified as “closed” where social ties and networks are very strong. The nature of these networks decreases the possibility of the likelihood of disclosure since information is likely to spread fast, then potential for stigmatization and marginalization following disclosure [28], [22]. However these social networks are also useful in providing social and emotional support for People Living With HIV and AIDS (PLWHA).

Adherence study findings in Tanzania are more likely to be different between urban and rural or semi-urban settings because most HIV care and treatment clinics are well established in urban settings. Rural environments have different demographic, socioeconomic and cultural characteristics. In order to develop effective public health interventions in the context of scaling ART services to rural areas, it is important to evaluate factors associated with non adherence among HIV-infected individuals residing in rural areas. The purpose of this study was to identify factors related to non adherence to ART in rural and semi-urban settings of Tanzania.

Patients and Methods

The study was conducted at Tumbi regional hospital and Chalinze health centre in Coast region between May 2008 and November 2008. Majority of the inhabitants of the hospital and health centre catchments areas are subsistence farmers and traders. They originated from different ethnic groups and are mainly Islam or Christians.

Since adherence to ART in most poor resource settings has been reported to be more than 95%, ascertainment of factors related to non-adherence is difficult. Therefore understanding these circumstances a case-control study design was chosen to be the best and applied.

We recruited adult patients aged 18-75 years old, who had been on ART for more than three months and agreed to participate in the interviews. The process of identification and selection of non adherence patients (Cases) and adherent (controls) involved use of pharmacy drug refill records. Patients with one or more missed drug refills in the past three months were listed and contacted for interviews. A structured questionnaire consisting questions on adherence to doses in the past 1-4 days, within the past week; adherence to time schedule; and the 30 days visual analogy scale (VAS) was used to determine the level of adherence to ART. Adherence to doses was calculated as doses taken over those prescribed. Adherence levels assessed using VAS was defined as full adherence if the patient marked 9.5 mm (95%) to 10 mm (100%) and non-adherence marked less than 9.5 mm (<95%) of the prescribed doses taken since last refill. Only patients who were found non adherence to all by less than 95% were defined as non-adherence cases. A total of 79 non-adherence patients were identified, and consented to participate in the study and matched by age and sex to three adherent controls.

Inclusion and exclusion criteria for cases and controls

Criteria	Cases	Controls
Age Duration on ART Clinic attendance record Level of ART adherence (Time schedule and dose)	=18 years More than 3 months* Attended same clinic in the last 6 months# Less than 95% in all	=18 years More than 3 months Attended same clinic in the last 6 months more than 95% in all
Patient functional status	Ambulatory	Ambulatory
Mental state	Competent and respond to questions	Competent and respond to questions

 # Time assumed adequate for patients to be familiar with providers and services at the clinic
***Time assumed to be adequate for patients to have experienced ART toxicity and side effects**

Data collection

A structured questionnaire was administered to all cases and controls during a scheduled appointment or routine clinic visits. The questionnaire was constructed using factors found to be associated with poor adherence to ART in similar settings in sub-Saharan Africa [23], [29], [30]. The key risk factors tested included: stigma, knowledge, provider-patient interaction, and selected social and behaviour factors. The questionnaire covered socio-demographic characteristics, social and behaviour factors. Eight items were developed to assess perceive availability of social support to cover four themes: emotional support (confidant), financial support, counselling and care during critical state. Depression was assessed using a ten items questionnaire adopted from the version of the Centres for Epidemiologic Studies Depression Scale (CES-D) accessible at *http:// www.chcr.brown.edu/pcoc/cesdscale.pdf.* Two groups of knowledge was assessed, knowledge of ART (benefits,

adherence, eligibility, names of drugs) and basic prevention methods (condom use, abstinence, avoid multiple sexual partners, avoid needle sharing). Stigma was assessed in two themes: negative self perception and discrimination experiences at home and in their community.

Statistical Analysis

Data were entered using Microsoft Office Access 2007, cleaned and transferred to Stata version 10 for analysis. Patient matched case-control pairs were created using Microsoft Office Excel 2007. Depression was scored as follows: 0 points rarely or none of the time (< 1 day); 1 point some or a little of the time (1-2 days); 2 points occasionally or a moderate amount of the time (3-4 days); and 3 points most or all of the time (5-7 days). A case or control was categorized to have full support if responded to have support in three or four of the themes, partial support was one to two, and no support if responded to have no one to provide any of the four support themes. Knowledge was classified as good if the respondents answered all the questions correctly. Distance was defined as the estimated distance of the patient residency from the study clinic measured in kilometres.

Univariate and multivariate conditional logistic regression was performed to identify factors associated with non adherence. The criteria for selection of variables possible for inclusion in multivariable analysis were based on p value of less than 5%. The strength of association was measured using matched Odds Ratios (mOR).

Ethical clearance

The study received scientific and ethical approval from the Muhimbili University of Health and Allied Sciences Research Ethics Review Board (Ref.No.MU/RP/AEC/Vol.XII/58). Permission was granted by Region, District and hospital authorities. Verbal informed consent for participation was obtained from patients using local Kiswahili language.

Results

Demographic characteristics

Three hundred and sixteen patients receiving ART participated in the study (79 cases and 237 matched controls). The mean (SD) age was 37.2 (8.5) years. About (64.2%) of the participants were females, (65.8%) were married or cohabiting and (71.8%) were Muslims. Majority of the patients completed primary education (73.4%), unemployed (74.1%) and (59.2%) reported an average monthly income of less than US$50 (Table 7 1). Individuals were more often living more than 5km away from the ART clinic (46.5% d”5km vs. 53.5% e”5km).There was no significant difference between cases and controls patients with respect to socio-demographic characteristics.

Univariate analysis

In a univariate analysis none of the socio-demographic determinants was found to be associated with non adherence to ART (Table 7 1). Persons with undisclosed HIV-positive status and those used alcohol were more likely to be non adherence (Table 7 3). Failure to disclose ones sero status was significantly associated with non adherence to ART (mOR 2.3, 95%CI 1.2-7.1). Similarly, individuals who disclosed not to their relatives were more than three times (mOR 3.3, 95%CI (1.3-8.5) likely to be non adherence to ART. The odds of patients who drink alcohol was almost two times greater compared to that of non alcohol drinkers (mOR 1.9, 95%CI 1.4-3.7). As shown in Table 7 3, taking care of under-five children, having episodes of depression and lack of support were not significantly related to non adherence. The proportion of patients without support was very low in both cases and controls (12.7% for cases and 11.4% for controls, respectively). The majority of cases and controls rarely experienced episodes of depression (65.8% in cases and 72.2% in controls).

A high proportion of controls (73.0%) never missed clinic appointments in the past three months. While more than half of cases (53.2%) missed clinic appointments due to lack of fare or other reasons. Failure to adhere to clinic appointment due to lack of fare and other reasons was found to be associated with non adherence to treatment (mOR 4.2, 95% CI 2.2-8.1 and mOR 2.1(1.2-4.2), respectively. Majority of patients (73.3% cases and 64.9% controls) used public minibuses to access ART services. A very small proportion of cases (8.9%) compared to controls (44.7%) reside within a walking distance to the ART clinic (Table 7 4).

The proportion of patients with good knowledge of HIV-prevention was high (68.3%) among controls compared to cases (50.6%). Patients with poor knowledge of basic HIV prevention were two times more likely to be non adherence compared to patients with good knowledge of ART (mOR 2.1, 95%CI 1.3-3.6). A high proportion of cases and controls (77.2% and 84.8%, respectively) had good knowledge of ART benefits, ART adherence and ART eligibility. Self perceived stigma was not associated with non adherence to ART (mOR 0.9, 95%CI 0.6-1.6) in this study population (Table 7 4).

Only one variable on patient-provider interaction; satisfied with providers, was related to suboptimal adherence to ART. Patients who reported not to be satisfied with health care providers were two times more likely to be poor adherence to ART (mOR 2.0, 95%CI 1.2-3.8). Spending long time with providers and frequent meetings with counsellors were not associated with adherence to ART (Table 7 5).

Multivariable analysis

In the final multivariate conditional logistic regression (Table 7 6) the following were identified as risk factors for non adherence: Missed clinic attendance due to lack of fare (adjusted mOR 6.4, 95%CI 2.6-15.9), missed clinic due to other reasons (adjusted

mOR 1.9, 95%CI 1.1-4.8), disclosure of HIV-positive status to other than relatives (adjusted mOR 5.2, 95%CI 1.4-19.5) and failure to disclose (adjusted mOR 2.8, 95%CI 0.6-13.5). Other factors included poor knowledge of basic HIV prevention methods (adjusted mOR 1.9, 95%CI 1.1-3.8), Alcohol intake (adjusted mOR 1.8, 95%CI 0.7-5.2) and unsatisfied with services provided (adjusted mOR 1.8, 95%CI 1.1-4.2).

Discussion

Previous studies on ART adherence in Tanzania have utilized cross-sectional and qualitative designs which lack the temporal order [26], [31], [32]. This case control study design is unique in this setting where adherence is reported to be more than 95% [33], [32], making non adherence a rare event. Thus case control study provides an effective approach to analyze the possible associations, and potentially determines more accurately which possible factors are directly related to non adherence, and which are merely related by a common cause.

In this study, we did not find an association between adherence to ART and socio-demographic characteristics. Consistent with previous studies on adherence to ART by gender, age and education levels [34]. The possible explanation for this finding is because we studied a homogeneous population with little socio-demographic and economic variations.

Social support may enhance adherence through encouragement, reassurance, reinforcement, systematic cues, bolstering of competence, and motivation or by masking the effect of stress, anxiety and depression. Social support was not significantly associated with adherence to ART in this study. This is in contrast to other previous studies where lack of support was related to sub optimal adherence to ART [25], [35], [36]. However the proportion of cases and controls without social support in this study population was very low which possibly overshadowed the effect of lack of social support. Equally depression was not

associated with poor adherence, again, because of low proportion of cases that experienced depressive symptoms occasionally (3-4 days) and in most days (5-7 days). In other settings depression has been an important predictor of poor adherence [29], [35], [36]. The low proportion of patients without social support and those who experienced depression symptoms can be explained by the common phenomenon and sometime is a requirement for ART patients in rural care and treatment clinics to have treatment assistants. A treatment assistant reminds the patient about drug intake times, collecting drugs at health facility and reporting side effects to the clinicians [6].

Stigma and discrimination against HIV-infected people was limited to perceived stigma in both cases and controls. Stigma was reported as self blame and fear to disclose one's HIV-positive status to other people which may result into gossips and lose of friends. Though we found no significant relationship between such perceived stigma and their treatment adherence, such stigma may lead to patients' unwillingness or fear to take medicine when other people were present. None of the study participants reported to have experienced stigma and social exclusion because of HIV-positive status. Other studies has highlighted stigma to be a barrier to adherence [37], [38]. The high burden of HIV-infection and more than two decades of AIDS related deaths in our study population have created awareness and perception evolution that reduced the magnitude of stigma which was experienced in first decade of HIV-epidemic. In this study, majority of patients disclosed their HIV-positive status to few family members and close relatives. Disclosure was significantly related to adherence, and this can explain the perceived stigma in this study population. Fear of disclosure has been documented to be among the barriers to adherence in African settings [16].

Alcohol consumption is one of the known barriers to ART adherence in both rural and urban settings [39], [37]. In some communities alcohol use is believed to temporarily alleviate HIV

related psychological problems [38]. Alcohol use can result into forgetfulness of the dose timing and dietary instructions that accompany some antiretroviral medications. Excessive alcohol use can cause liver damage and exacerbate antiretroviral drug side effects. In agreement with these studies alcohol use was a significant predictor of non adherence to ART in the present study. Our assessment of alcohol intake was limited to self-report of consuming alcoholic beverages two or more times in a week, there were no more questions to quantify the amount consumed. This can limit the strength of association between alcohol intake and adherence to ART. However these findings indicate the importance of regular alcohol counselling and education related to ART adherence among HIV-patients on ART.

World Health Organization included free access to ART at the point of service delivery as a component of its public health approach for reaching universal access in low income countries [3]. Although coverage rates continue to increase but most rural residents still have to travel long distances to access ART services. Transport costs can pose an important barrier to clinic attendances and ultimately poor adherence to ART [23], [22]. In this study, most of the patients needed some form of transport to reach ART clinic. Majority of cases and controls used public minibuses and therefore had to pay for the transport. We found that lack of transport money coupled with other reasons significantly associated with non adherence. Adaptation of the tuberculosis Direct Observed Therapy as a strategy to improve adherence to ART in settings like this need to address transport cost challenges. Dispensing of ARVs in quarterly bases after the first three months of monitoring adherence and toxicity, can reduce the transport costs and encourage adherence success. Where feasible government subsidized transport can reduce costs to the patients substantially [22]. The ongoing decentralization of ART services to rural health facilities

subsequently will reduce the transport needs for majority of the patients in Tanzania.

Knowledge of basic HIV-infection prevention measures was significantly associated with adherence to treatment. But knowledge of ART benefits, adherence requirements and eligibility was not related to adherence to ART. This contrasting finding is explained by the high level of HIV-infection prevention awareness in the communities, and acts as a motivation of ART adherence. Majority of the patients responded to two questions that assessed knowledge of ART benefits that ARVs prolong life and protect against opportunistic infections, compared to questions on eligibility, adherence schedules, doses and names of drugs. To remember the complicated names of ARVs, a high level of education is required; no wonder in some settings education level is associated with adherence [16]. However, in practice lack of information and communication about treatment is the actual barrier to treatment [37]. Although delivery of ART counselling and education in our study population is done in local spoken language, but there is a need to explore the content of Information, Education and Communication (IEC) materials used and how local disease concepts are communicated. Understanding and incorporating local peoples' perception and feelings towards HIV/AIDS in developing IEC materials is one of the ways to impact ART knowledge to PLHA and improve communication between patients and providers.

Good patient-provider relationship and patients' satisfaction with health care services have shown positive correlation with adherence to ART in some settings [40], [41]. Regular contact with either counsellors or long time spend with providers were not associated with adherence. But, patients who felt not satisfied with the time they spend with providers were non adherent to treatment. Such patients probably were unable to express their concerns about medications. In this setting continued patients counselling tailored to individual needs would improve adherence.

ART patients taking care of children below 5 years may forget to take medications due to being busy or stress of caring for the child. The lack of statistical significant relationship between caring of under-five children and adherence to ART is because the study sample is not big enough to segregate this variable between male and females. Traditionally, daily care of children is the duty of the females.

Interpretation of our study findings must be taken in the light of its limitations. The time set of three months adherence was too short to capture non-adherence risk factors dynamics. Temporary changes of risk factors making cases or controls become controls or cases might have affected the analysis but we had to set the time limit considering the possibility of recall bias.

Conclusions

We found that patient-important barriers to good adherence are fear of disclosure one's HIV positive status, use of alcohol, lack of good knowledge of basic prevention methods, unsatisfied with providers and transport costs to ART clinic. These findings explain that adherence is a dynamic process that varies depending on region or cohort specific adherence factors. Adherence improvement strategies need to take into consideration site specific adherence determinants, patient experiences and concerns. Dispensing of ARVs in quarterly bases can reduce the transport costs and encourage adherence success for patients residing far from ART clinics. But more research is needed on ART adherence and virological suppression in patients residing far away from ART clinics who may require a three months ARVs supplies.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BI Participated in conception and design of the study. He also coordinated all activities pertaining to collection and management of data, analysis and interpretation of data. He has been involved in drafting the manuscript and revising it.

MT has been involved in conception and design of the study; drafting the manuscript and revising it critically and has given the final approval of the version to be published.

BJ has been involved in drafting the manuscript and revising it critically.

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References

1. Tanzania Ministry of Health and Social Welfare, National Guidelines for the Management of HIV and AIDS, National AIDS Control Programme (NACP) 3rd edition 2007

2. World Health Organization; AIDS epidemic update: December 2006

3. UNAIDS/WHO/ UNICEF Epidemiological fact sheets on HIV and AIDS [Internet]. [cited 2010 May 24];Available from: [http://www.unaids.org/en/KnowledgeCentre/HIVData/Epidemiology/epifactsheets.asp]

4. Somi G, Matee M, Swai R, Lyamuya E, Killewo J, Kwesigabo G, et al. Estimating and projecting HIV prevalence

and AIDS deaths in Tanzania using antenatal surveillance data. BMC Public Health. 2006;6(1):120.

5. The Global Fund to Fight AIDS, Tuberculosis and Malaria 2010 [http://portfolio.theglobalfund.org/Country/Index/TNZ?lang=en]

6. Stoeckle M, Mchomvu R, Hatz C, Battegay M, Aris EA, Mshinda H, and Tanner M. Moving up from 3 by 5. Lancet Infect Dis. 2006 Aug;6(8):460-461.

7. Braitstein P. Antiretroviral Therapy in Lower Income Countries (ART-LINC) collaboration. ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. LANCET (N AM ED). 2006;367(9513):817.

8. Attaran A. Adherence to HAART: Africans Take Medicines More Faithfully than North Americans. PLoS Med. 2007 Feb;4(2).

9. Nilsson Schönnesson L, Williams M, Ross M, Bratt G, Keel B. Factors Associated with Suboptimal Antiretroviral Therapy Adherence to Dose, Schedule, and Dietary Instructions. AIDS and Behaviour. 2007 Mar 1;11(2):175-183.

10. Ledergerber B, others. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. The Lancet. 2004;364(9428):51–62.

11. Zaccarelli M, Tozzi V, Lorenzini P, Trotta MP, Forbici F, Visco-Comandini U, Gori C, Narciso P Perno CF, Antinori A. Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients. Aids. 2005;19(10):1081.

12. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clinical Infectious Diseases. 2003;37:1112–1118.

13. Harris RJ, Sterne JA, Abgrall S, Dabis F, Reiss P, Saag M, Phillips AM, Chene G, Gill JM,Justice AC, Rockstron J, Sabin CA, Egger M, Bucher HC, Hogg RS, Monforte A, May M. Prognostic importance of anaemia in HIV type-1-infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies. Antiviral therapy. 2008;13(8):959-67.

14. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to Highly Active Antiretroviral Therapy Assessed by Pharmacy Claims Predicts Survival in HIV-Infected South African Adults. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2006 9;43(1):78-84.

15. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wgener, Singh N. Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection. Annals of Internal Medicine. 2000 Jul 4;133(1):21-30.

16. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, Rachlis B, Wu P, Cooper C, Thabane L, Wilson K, Guyatt G, Bangsberg. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006 Aug 9;296(6):679-690.

17. Pujari SN, Patel AK, Naik E, Patel KK, Dravid A, Patel JK, Manne AA, Bhagat S. Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2004;37(5):1566.

18. Ammassari A, Murri R, Pezzotti P, Trotta MP, Ravasio L, De Longis P, Caputo SL, Narciso P, Pauluzzi S, Carosi G. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2001;28(5):445.

19. Ickovics JR, Meade CS. Adherence to antiretroviral therapy among patients with HIV: a critical link between behavioural and biomedical sciences. J. Acquir. Immune Defic. Syndr. 2002 Dec 15;31 Suppl 3:S98-102.

20. Coetzee D, Boulle A, Hildebrand K, Asselman V, Van Cutsem G, Goemaere E. Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa. AIDS. 2004 Jun;18 Suppl 3:S27-31.

21. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugyenyi PN, Bangsberg DR. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. Int J STD AIDS. 2005 Jan;16(1):38-41.

22. Colebunders R, Kamya M, Semitala F, Castelnuovo B, Katabira E, McAdam K. Free Antiretrovirals Must Not Be Restricted Only to Treatment-Naive Patients. PLoS Med. 2005 Oct;2(10).

23. Weidle PJ, Wamai N, Solberg P, Liechty C, Sendagala S, Were W, Mermin J, Buchazz K, Behumbiliize P, Ransom RL, Bunnell R. Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda. Lancet. 2006 Nov 4;368(9547):1587-1594.

24. Chesney MA. Factors affecting adherence to antiretroviral therapy. Clin. Infect. Dis. 2000 Jun;30 Suppl 2:S171-176.

25. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. J. Acquir. Immune Defic. Syndr. 2001 Sep 1;28(1):47-58.

26. Ware NC, Idoko J, Kaaya S, Biraro IA, Wyatt MA, Agbaji O, Challamilla G, Bangsberg DR. Explaining adherence success in sub-Saharan Africa: an ethnographic study. PLoS Med. 2009 Jan 27;6(1):e11.

27. Mossdorf E, Stoeckle M, Vincenz A, Mwaigomole EG, Chiweka E, Kibatala P, Urassa H, Abdulla S, Elzi L, Tanner M, Furrer H, Hatz C, Battegay M. Impact of a national HIV voluntary counselling and testing (VCT) campaign on VCT in a rural hospital in Tanzania. Trop. Med. Int. Health. 2010 May;15(5):567-573.

28. Paxton S. Public disclosure of serostatus — the impact on HIV-positive people. Sex Health Exch. 2000;(1):13-14.

29. Amberbir A, Woldemichael K, Getachew S, Girma B, Deribe K. Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in Southwest Ethiopia. BMC Public Health. 2008;8:265-265.

30. Mshana GH, Wamoyi J, Busza J, Zaba B, Changalucha J, Kaluvya S, Urassa M. Barriers to Accessing Antiretroviral Therapy in Kisesa, Tanzania: A Qualitative Study of Early Rural Referrals to the National Program. AIDS Patient Care and STDs. 2006 9;20(9):649-657.

31. Roura M, Wringe A, Busza J, Nhandi B, Mbata D, Zaba B, Urassa M. “Just like fever”: a qualitative study on the impact of antiretroviral provision on the normalisation of HIV in rural Tanzania and its implications for prevention. BMC Int Health Hum Rights. 2009;9:22.

32. Minzi OMS, Naazneen AS. Validation of self-report and hospital pill count using unannounced home pill count as methods for determination of adherence to antiretroviral therapy. Tanzan J Health Res. 2008 Apr;10(2):84-88.

33. Mugusi F, Mugusi S, Bakari M, Hejdemann B, Josiah R, Janabi M, Aboud S, Swai H, Biberfeld G, Pallangyo K, Sandstrom E. Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience. Trop. Med. Int. Health. 2009 Oct;14(10):1226-1232.

34. Ammassari A, Trotta MP, Murri R, Castelli F, Narciso P, Noto P, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. J. Acquir. Immune Defic. Syndr. 2002 Dec 15;31 Suppl 3:S123-127.

35. Catz SL, Kelly JA, Bogart LM, Benotsch EG, McAuliffe TL. Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. Health Psychol. 2000 Mar;19(2):124-133.

36. Murphy DA, Marelich WD, Hoffman D, Steers WN. Predictors of antiretroviral adherence. AIDS Care. 2004 May;16(4):471-484.

37. Sanjobo N, Frich JC, Fretheim A. Barriers and facilitators to patients' adherence to antiretroviral treatment in Zambia: a qualitative study. SAHARA J. 2008 Sep;5(3):136-143.

38. Dahab M, Charalambous S, Hamilton R, Fielding K, Kielmann K, Churchyard GJ, Grant AD. "That is why I stopped the ART": patients' & providers' perspectives on barriers to and enablers of HIV treatment adherence in a South African workplace programme. BMC Public Health. 2008;8:63.

39. Peltzer K, Friend-du Preez N, Ramlagan S, Anderson J. Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa. BMC Public Health. 2010;10:111.

40. Mostashari F, Riley E, Selwyn PA, Altice FL. Acceptance and adherence with antiretroviral therapy among HIV-infected women in a correctional facility. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 1998 Aug 1;18(4):341-348.

41. Watt MH, Maman S, Golin CE, Earp JA, Eng E, Bangdiwala SI, Jacobson M. Factors associated with self-reported adherence to antiretroviral therapy in a Tanzanian setting. AIDS Care. 2010 Mar;22(3):381-389.

Table 7. 1: Baseline characteristics of the study participants
Characteristic

Characteristic	
Total n (%)	316(100)
Median age, years(IQR)	37(10.5)
Female gender, %	64.2
Married or cohabiting,%	65.8
Religion-Islam, %	71.8
$CD4^+$ T-cell count*	64.2
$CD4^+$ T-cell count, median(IQR)	329(311)
Duration on ART, %	
3-12 months	34.5
13-24 months	29.1
≥25 months	36.4
Unemployed, %	74.1
Monthly income (US$), %	
<50	59.2
50-150	29.4
>150	11.4
Distance to the ART clinic, ≥5km	46.5%

Table 7. 2: Socio-demographic determinants of Antiretroviral Therapy adherence among cases and controls

Characteristics	Frequency among Controls n (%)	Frequency among Cases n (%)	Univariate mOR (95% CI)
All patients	237(75%)	79(25%)	-
Age (years) groups*			
18-29	39(16.5)	14(17.7)	2.19(0.2-22.6)
30-39	159(67.0)	53(67.1)	Reference
>39	39(16.5)	12(15.2)	0.96(0.4-2.3)
Sex			
Male	85(35.9)	28(35.4)	Reference
Female	152(64.1)	51(64.6)	1.3(0.2-9.5)
Marital status			
Married/cohabiting	162(68.3)	46(58.2)	Reference
Single/divorced/widow/separated	75(31.7)	33(41.8)	1.5(0.9-2.6)
Education level			
No education	41(17.3)	15(18.9)	1.2(0.6-2.3)
Primary	176(74.3)	56(71.0)	Reference
Secondary/college	20(8.4)	8(10.1)	1.2(0.5-2.9)
Religion			
Islam	173(73.0)	54(68.4)	Reference
Christian	64(27.0)	25(31.6)	1.2(0.7-2.1)
Main source of income			
Employed	60(25.3)	22(27.8)	Reference
Unemployed	177(74.7)	57(72.2)	1.1(0.6-2.0)
Average monthly Income US$			
<50	144(60.8)	43(54.4)	Reference
50-150	66(27.8)	27(34.2)	1.4(0.8-2.5)
>150	27(11.4)	9(11.4)	1.1(0.5-2.7)

Test for trend across ordered groups Z=-0.07, p=0.95

Table 7.3: Social and behavioural factors with their relationship to adherence to Antiretroviral Therapy among cases and controls

	Frequency among		Univariate
Variable	**Controls: n (%)**	**Cases: n (%)**	**mOR (95% CI)**
All patients	237(75%)	79(25%)	-
Taking care of <5 children			
Cares no child	76(32.1)	22(27.8)	Reference
Cares 1-2 children	96(40.5)	44(55.7)	1.5(0.8-2.7)
Cares >2 children	65(27.4)	13(16.5)	0.7(0.3-1.5)
Availability of support			
Full support	115(48.5)	32(40.5)	Reference
Partial support	92(38.8)	38(48.1)	1.5(0.9-2.5)
No support	30(12.7)	9(11.4)	1.1(0.8-1.6)
Depression in the past week			
Rarely (<1 day)	171(72.2)	52(65.8)	Reference
Some days (1-2 days)	26(10.9)	14(17.7)	1.8(0.9-3.7)
Occasionally (3-4 days)	23(9.7)	8(10.2)	1.1(0.5-2.6)
Most days (5-7 days)	17(7.2)	5(6.3)	1.0 (0.4-2.9)
Disclosure Status			
Disclosed to many people	61(25.7)	17(21.5)	Reference
Disclosed to 1-2 relatives	146(61.6)	42(53.2)	1.0(0.5-1.9)
Disclosed not to relatives	19(8.1)	14(17.7)	3.3(1.3-8.5)
Not disclosed to anyone	11(4.6)	6(7.6)	2.3(1.2-7.1)
Drinks alcohol			
No	206(76.9)	31(64.6)	Reference
Yes	62(23.1)	17(35.4)	1.9(1.4-3.7)

Table 7. 4: Treatment and care seeking influencing factors and their association with adherence to Antiretroviral Therapy among cases and controls

Variable	Frequency among Controls: n (%)	Frequency among Cases: n (%)	Univariate mOR (95% CI)
Self perceived stigma			
No	129(54.4)	35(44.3)	Reference
Yes	108(45.6)	44(55.7)	0.9(0.6-1.6)
ART knowledge			
Good	201(84.8)	61(77.2)	Reference
Poor	36(15.2)	18(22.8)	1.6(0.9-3.0)
Knowledge of basic prevention methods			
Good	162(68.3)	40(50.6)	Reference
Poor	75(31.7)	39(49.4)	2.1(1.3-3.6)
Distance from ART clinic (Km)			
Less than 6 km	106(44.7)	41(51.9)	Reference
6 km and more	131(55.3)	38(48.1)	0.7(0.4-1.2)
Type of transport used to clinic			
Walk	24(10.1)	7(8.9)	Reference
Bicycle	16(6.8)	7(8.9)	1.5(0.4-5.4)
Motorcycle	33(13.9)	7(8.9)	0.7(0.2-2.4)
Bus	164(69.2)	58(73.3)	1.2(0.5-2.9)
Duration from HIV +test to seeking care			
Within month of test	154(64.9)	47(59.5)	Reference
1-12 month after test	67(28.3)	23(29.1)	1.1(0.6-1.9)
>12 months after test	16(6.8)	9(11.4)	1.8(0.8-4.2)
Adherence to clinic attendances			
Never missed	173(73.0)	37(46.8)	Reference
Missed due to lack of fare	33(13.9)	28(35.5)	4.2(2.2-8.1)
Missed due to other reasons	31(13.1)	14(17.7)	2.1(1.2-4.2)
Duration on ART (in months)			
3-12	76(32.1)	33(41.8)	Reference
13-24	71(29.9)	21(26.6)	0.7(0.4-1.3)
≥25	90(38.0)	25(31.7)	0.6(0.3-1.2)

Table 7. 5: Patient-provider interaction factors and their relationship with Antiretroviral Therapy adherence status

Variable	Frequency among Controls	Frequency among Cases	Univariate mOR (95%CI)
Meeting with counsellors in past 6 months			
Not at all	179(75.5)	58(73.4)	Reference
1-5 times	49(20.7)	18(22.8)	1.2(0.6-2.2)
More than 5 times	9(3.8)	3(3.8)	1.2(0.3-4.7)
Time spend with provider			
Less than10 minutes	68(28.8)	18(22.8)	Reference
More than 10 minutes	168(71.2)	61(77.2)	0.7(0.4-1.3)
Satisfied with providers			
Yes	195(83.0)	57(72.1)	Reference
No	40(17.0)	22(27.9)	2.0(1.2-3.8)

Table 7. 6: Final multivariable conditional logistic regression model for the factors associated with non-adherence to Antiretroviral Therapy

Factors	Adjusted mOR(95% CI)*	*P*-value
Adherence to clinic attendances		
Never missed	Reference	
Missed due to lack of fare	6.4 (2.6-15.9)	<0.001
Missed due to other reasons	1.9 (1.1-4.8)	0.05
Disclosure Status		
Disclosed to many people	Reference	
Disclosed to 1-2 relatives	1.2 (0.5-2.7)	0.642
Disclosed not to relatives	5.2 (1.4-19.5)	0.015
Not disclosed to anyone	2.8 (0.6-13.5)	0.201
Drinks alcohol		
No	Reference	
Yes	1.8 (0.7-5.2)	0.043
Knowledge of basic prevention methods		
Good	Reference	
Poor	1.9(1.1-3.8)	0.050
Satisfied with providers services provided, time spend and issues discussed		
Yes	Reference	
No	1.8(1.1-4.2)	0.034

***Adjusted to all variables in Table 7 2, Table 7 3, Table 7 4, Table 7 5**

Figure 8. 1: The study scientist examining a patient at Tumbi Hospital

Chapter 8: Lessons from Chalinze Health Centre model of HIV-case management in resource limited set tings of Tanzania

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Abstract

Background

Implementation of ART services at Health centres in Tanzania were delayed due to several reasons including shortage of qualified staff, inadequate infrastructure and logistics problems. However, patients from peripheral (rural) areas experienced difficulties in accessing ART services due to long distances from clinics. NACP and NGOs embarked on ART services scale-up program aimed at improved ART availability and accessibility. Through this program ART services were established at Health Centres and selected dispensaries. However, no previous documented experiences existed at country level to guide provision of services. Therefore, this study was designed to gather experiences and share lessons learnt with other health care providers and program implementing partners.

Methods

This was a descriptive cross-sectional study involved patients enrolled to ART services between May 2007 and April 2009. Data collection involved observation of health providers' performance and retrospective ART and Care patients' registers review.

Results

During the study period, 611 care and 284 ART patients were attended. Majority of patients 762/895 (85.1%) were adults aged 25-45 years, while children were 27/611 (4.4%) pre ART and 16/284 (5.6%) ART. In total 550/895 (61.5%) patients had CD4+T lymphocytes d"350/µl the cut-off point for initiating ART. The frequency of symptoms was noted to significantly decrease with increasing CD4 counts ($p<0.001$). However, numbness, parotid enlargement and genital discharge were not related to patient level of CD4+T-lymphocytes counts. Papular Pruritic eruptions

98/282(34.8%), Tuberculosis 86/282(30.5%) and Oesophageal Candidiasis 37/282(13.1) were the most diagnosed AIDS defining illnesses. Sixteen patients on care died and 30 were lost to follow up. Overall the clinical management was poorly performed.

Conclusions

In conclusion ART services can successively be provided at health centre level and encourages HIV-infected persons to seek care. However, clinicians need regular clinical mentorship and supportive supervision.

Introduction

Tanzania HIV/AIDS care and treatment services were initially focused at District and other high level health facilities (MOH 2005). Health centres were left out due to several reasons including lack of qualified clinical staff, lack of adequate infrastructure and supply logistics problems (Wyss 2004), (Katabira & Oelrichs 2007), (Kober & Van Damme 2004). However, many patients from remote rural areas experienced difficulties in accessing care and treatment in District hospitals. The majority of patients in rural areas travel long distances to reach District hospitals and endure long waiting times in queues at the clinics (Hardon et al. 2007). As a result, patients fail to follow routine appointments and failed to adhere to appointment schedules for ART treatment. Tanzania National AIDS Control Program (NACP) challenged with the rapid increase of AIDS patients in District and referral hospitals recognized the need to establish ART services at Health Centres and other selected lower health facilities aimed at improving access and adherence to ART, reduction of loss to follow up and stigma (MOH 2005). Consequently, NACP and Non-Governmental Organizations (NGO) implemented a regionalization approach aimed at increasing the speed of ART scaling-up process to cover the entire country. Each NGO was assigned specific regions to implement ART services and related programs. A national ART accreditation protocol was developed and used to assess health care facility infrastructure capacity, available human resources and potential volume of HIV/AIDS patients. Through this process Chalinze health centre was accredited to provide ART services which were commenced in May 2007.

A typical Health Centre has 15 bed capacities and is managed by an Assistant Medical officer supported by medical assistants and assistant nurses. Laboratory services at the health centre are limited to basic haemoglobin, sputum, urine and stool

microscopic examinations. Usually a Health Centre serves as a third level of health services referral hierarchy, followed by dispensary and village health post. A Health Centre is expected to cater for a population of 50,000 people which is approximately the population of one administrative division in Tanzania.

However concerns have been raised about the quality of ART services delivered in Health centres due to inadequate human resource capacity and lack of laboratory facilities for monitoring CD_4 + T-lymphocytes testing (Van Damme et al. 2006), (Kober & Van Damme 2004), (Katabira & Oelrichs 2007). Furthermore, establishment of care and treatment clinics at lower levels of health care facilities poses challenges on the health system ability to pull enough resources (Morrison 2002) to cope with increased logistics demands, supply chain management and supportive supervision. Such challenges can be addressed by health centre patient treatment cohort analysis. Currently there is no published data on health centre experiences of delivering ART services in Tanzania. This study therefore, was designed to gather experiences and share lessons learnt with other health care providers and program implementing partners.

The major objectives of this study were: (1) to describe HIV and AIDS case management at a rural health centre level in Tanzania, (2) to assess short-term outcomes of patients attending care and treatment at a health centre, (3) to describe experiences and lessons learned in the process of implementing ART in a rural health centre in Tanzania.

Methods

2.1. Setting

Chalinze Health Centre is the largest rural Health Centre in Bagamoyo District in Pwani Region, Eastern Tanzania. The health centre is located at Chalinze town, 80 km and 70 km from Bagamoyo District and Tumbi Region Hospitals, respectively.

The Health centre serves inhabitants of seven villages around Chalinze town with approximately population of 300,000 people. Most residents are farmers and small scale traders and rely on health services delivered by the Health centre. The HIV-1 seroprevalence in 2007 was 15%. The health centre started offering ART services in May 2007 with financial support from President's Emergency Plan for AIDS Relief (PEPFAR) and technical support from Columbia University Mailman School of Public Health (ICAP). ICAP provided clinical training and mentorship, renovation of the health centre building to create rooms for ART services, procuring equipment and supplies, and establishing systems to support laboratory services and data collection. The staffs at health centre involved with ART services delivery were trained for two weeks using training modules accredited by Tanzania National AIDS Control program. ART treatment started under the supervision and mentorship of experienced Doctors and Nursing officers from Tumbi Regional Hospital in collaboration with ICAP staff. The ART start-up clinical team comprised of one clinical officer (with diploma in clinical medicine), two medical attendants (nurses), one pharmaceutical assistant and a data cum registry clerk. By the end of April 2009, 858 adults and children were enrolled for ART services.

2.2 Clinical services process

ART services are provided daily Monday to Friday, two days in a week are dedicated to newly enrolled patients to receive counselling, clinical examination and laboratory evaluation. Laboratory services at the health centre are limited to basic haemoglobin, blood, urine, sputum and stool microscopic examinations. CD4+ T lymphocytes, haematology and biochemistry analysis were sent to Tumbi regional hospital two times every week and results were obtained in the following week. Reasonable referral networks existed with dispensaries, village health posts, Bagamoyo District and Tumbi Regional Hospital.

Patients starting to use ARVs are given an appointment according to treatment guideline to be seen at the clinic after two weeks. From then on, provided there are no side effects, patients are seen and given ARVs at 4 weeks intervals. Clinical officers are mainly responsible for patients' clinical examination, treatment initiation, regimen changes and follow-up patient clinical evaluation. Assistant nurses provide counselling according to standardized protocols.

Patients were eligible for ARVs if were symptomatic (WHO clinical stage III or IV), and have CD4+ T lymphocytes count of <200µl. Patients are required to meet a number of additional criteria including: completing ART counselling sessions, nominating a 'treatment assistant' to assist with adherence. The first-line ART regimen in Tanzania is a fixed-dose combination of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) (Triomune). In case of d4T- and NVP-related side effects, the respective alternatives are zidovudine (AZT) and efavirenz (EFV). ART is offered free of charge in all public facilities in Tanzania, including Chalinze health centre.

ART monitoring is done using standardized National monitoring tools which include care and ART registers. Patients are issued identification cards, upon registration, bearing demographic characteristics and dispensed ARVs regimen or Cotrimoxazole and appointment date for the subsequent clinic visits. Standardized treatment outcomes are monitored every month in the patient master cards and updated each month in the ART register; thereafter quarterly reports are sent to the Ministry of Health.

2.3. Data collection

Two different methods of data collection were used; non-participant observations of health providers' performance and retrospective pre ART and ART registers reviews. Health providers' performance indicators are summarized in the following

Table 8 1. The researcher took the role of non-participant observer in the consultation room. Verbal Informed Consent was obtained from patients and the attending clinicians. Observation check list was used to systematically document the clinician's actions and approaches. The check list was developed based on the National HIV and AIDS treatment guidelines **(**MOH 2005**)** and contained minimum set of actions which must be carried out for the care given to be classified as adequate quality care.

Table 8. 1: Clinical actions assessed by observations

Score	History taking	Physical examination	Ordering laboratory tests	Prescribing therapy	Patient education
Excellent	4	4	4	4	4
Good	3	3	3	3	3
Satisfactory	2	2	2	2	2
Inadequate	1	1	1	1	1
Never done	0	0	0	0	0

A sample of 40 patients categorized in two groups of newly enrolled (first clinic attendees) and continuing clients were conveniently selected for this assessment. This is to allow collection of comparable and triangulation of data.

The concern, however, is that people who know that they are being observed may change their behaviour. This challenge was addressed by making observation to last long enough (2 months), thereby making clinicians to eventually revert to their normal behaviour. It has been established that few people have the capacity to keep up a "perfect" artificial behaviour for extended periods.

Data collected from pre ART and ART registers reviews included demographic characteristics, signs and symptoms at first enrolment to the clinic, laboratory results, treatment regimen start and stop dates and the reason for change, and reasons for treatment termination. Patients case report forms (CT2) which

records patients demographic and clinical parameters, facility and patient registration codes and clinic visit dates were reviewed.

2.3. Data analysis

Data was entered into Microsoft ®Access, and analyzed using Stata Intercooled version 9. The observation scores were compiled for each clinical process and the proportion of cases in which it was executed. A minimum set of actions were set according to the category of the patients (New or follow up case) all of which must be carried out for a case to have been handled with adequate quality of care. The cumulative personal years of follow-up was calculated from the date of enrolment to cut-off point of follow-up or lost to follow-up or death of the pre ART patients. Lost to follow-up was defined as three or more consecutive months since last scheduled appointment. Patients taking antiretroviral drugs (ARVs) were excluded from mortality rate analysis because no death occurred and ARVs would confound findings.

Ethical clearance

The study received scientific and ethical approval from the Muhimbili University of Health and Allied Sciences Research Ethics Review Board (Ref.No.MU/RP/AEC/Vol.XII/58) Permission was granted by Region, District and health centre authorities. Informed consent for participation was obtained from patients using Kiswahili language.

Results

Over a period of about 25 months, a total of 895 pre ART and ART patients were attended at Chalinze health centre. Of the ART patients 284 were still active during the study period and provided complete data for analysis. Thirty (4.9%) patients on care and 55 (19.4%) on ART were lost to follow-up. The quarterly cumulative numbers of patients enrolled and retained into care and ART are displayed in details in Figure 8 1.

Patients' characteristics are detailed in Table 8 2. Majority of patients were adults' aged between 25 to 45 years. Only 27/611 (4.4%) pre ART and 16/284 (5.6%) ART children were enrolled during the study period. Majority of the patients were females 622/895 (69.5%), males had higher mean weight compared to females (mean 53.3 and 46.3 respectively).Most patients reported to be working 605/895(67.6%) and 281/895(31.4%) were ambulatory. At presentation to the clinic, majority of patients 550/895 (61.5%) had CD4+T-lymphocytesd"350 and 531/895(59.3%) in WHO clinical stages III/IV. Sixteen patients on care died at different times during the study period, contributing to mortality rate of 2.13(95%CI 1.31 to 3.48) per 100 patient-years, and 23/284 (8.1%) ART patients died, resulting onto mortality rate of 0.042(95%CI 0.01-1.01). More than half (152/238(63.9%)) of patients on ART had CD4+T cells<200/µl.

A wide range of signs and symptoms occurred and were recorded at enrolment. Patients whose CD4+T-lymphocytes counts were low had more symptoms and signs than those with relatively higher counts. The frequency of symptoms was noted to significantly decrease with increasing CD4 counts. However, numbness, parotid enlargement and genital discharge were not related to patient level of CD4+T-lymphocytes counts. Many patients reported weight loss, skin itching or rashes which was followed by fever, body weakness and productive cough. Chronic diarrhoea was found in only 47/895(5.2%) patients was significantly related to CD4+T-lymphocytes counts levels (p=0.02). (Table 8 3).

Majority of patients enrolled for care received HIV test from Voluntary Counselling and testing centres (VCT) (39.4%), followed by outpatient (24.2%) and MCH/PMTCT (12.6%) (Figure 8 2). Patients at the outpatient, inpatient and Tuberculosis units were tested through provider initiated testing and counselling program. Surprising no patients were HIV-tested at sexually

transmitted infection clinic (STI clinic) despite of training all clinical staff at the centre in provision HIV testing.

Overall 282 cases of AIDS defining illnesses (ADIs) were diagnosed and treated during the study period. The most frequent ADIs cases were Papular Pruritic eruptions 98/282(34.8%), Tuberculosis 86/282(30.5%) and Oesophageal Candidiasis 37/282(13.1). Less common ADIs were Herpes zoster 16/282(5.7%), HIV encephalopathy 16/282(5.7%), HIV wasting syndrome 15/282(5.3%), Kaposi's sarcoma 11/282(3.9%) and Pneumocystis Pneumonia 3/282(1.1%) (Figure 8 4).

Clinicians were trained to use three methods to evaluate patients' eligibility to start ART: WHO clinical staging, CD4+T-cells count or combination of these two. About 45.7% of patients were evaluated using CD4+T-cells counts while WHO clinical staging only was used in 39.1% of patients, and both methods were applied in 15.2% of patients (Figure 8 3).

The average consultation time was 4 minutes. Seventy-five percents of the consultations lasted less than 5 minutes and none more than 10 minutes. All consultations were characterized by inadequate history taking and lacked explanations of the disease, prescription and or the ordered laboratory investigations. Physical examination in terms of inspection and palpation head to toe was performed in 39% of the patients in a sitting position and 6% were asked to lie on examination bed. Unless the patient volunteered to show a lesion on the body, most often clinicians never solicited for abnormalities. Most prescriptions were repetitions of the previous medications and not the diagnosis of the day. Occasionally patients would remind the clinician to prescribe additional medicines for the new complaint.

Discussion

Our study presents quantitative and qualitative findings; the qualitative findings were enlisted through observation of health

care providers but did not collect data on patients' perceptions of the services provided. We found that clinical management was poorly performed, marked with inadequate physical examination, inaccurate history taking and short consultation times. Despite expectations that clinical practice could be improved after ART training, we did not find any evidence to support such hypothesis. This study is not the first article to report on poor technical quality of care: similar practices have been reported by studies conducted in primary health care facilities in Tanzania in relation to malaria case management (Gilson et al, 1993) (Nsimba et al. 2002). Clinical mentorship and regular supportive supervision programs need to be strengthened in order to shape the clinical practice in peripheral health care facilities.

At Chalinze health centre we found an excellent referral system networks used to access ART services by patients from nearby dispensaries and the transportation of samples to Tumbi hospital laboratory. Similar referral mechanisms can be established in any sites linking HIV-infected patients with care and treatment centres.

The large number of patients enrolled for HIV/AIDS care and treatment at Chalinze health centre within the short period of 25 months is alarming. However, it may be the result of increased awareness of ART health benefits, decreased HIV stigma due to ART availability close to patients' homes and the big burden of AIDS in rural population (Posse et al. 2008). HIV/AIDS associated mortality rates in rural areas of Tanzania is known to be more than 15 times compared to HIV-negative deaths rates (M. Urassa et al. 2001). ART services availability within short distances encourages patients who were to travel for long distances or even days to seek ART care and treatment. The proximity to services motivates entry to care and encourages retention in care.

Our findings point to already established facts that, it is possible to provide ART services in rural resource limited settings using existing health care workers after up-grading their skills (Wyss 2004). Despite of the weakness and short comings documented by this study, clinic attendance was growing steadily, an indication of high demand for services and some degree of patients' satisfaction was noted with the services rendered. Patients studied experienced numerous signs and symptoms whereby; cough, fever and non-specific skin rashes were the most frequently reported. It is important to note that persistent cough is becoming a major sign of AIDS overtaking weight loss and chronic diarrhoea. Profound weight loss, chronic diarrhoea and prolonged fevers were noted to mark major signs and symptoms of AIDS in the pre-ARVs era (WHO 1987, (Piot et al. 1984). In addition, pain in terms of headache, abdominal pain and burning or burning/tingling sensations, when both symptoms are considered across the pain trajectory becomes one of the most frequently reported symptoms. Pain has been reported in other settings as one of the most frequent symptoms (Bhengu et al. 2009), (Sukati et al. 2005). This finding suggests that pain management must be prioritized by clinicians caring for HIV/ AIDS patients.

The number of children enrolled was rather lower than the 12% program set target. However, diagnosis and provision of ART in HIV-infected children is more complex than in adults. Diagnosis of exposed infants up to 18 months of age requires HIV-p24, RNA or DNA polymerase chain reaction tests (Lyamuya et al. 1996). And also CD4+T cell percentage is required instead of absolute CD4+T cell count for older children which were not available during the study period. Therefore enrolment of children was only based on clinical manifestation and HIV antibody positive tests. This way many HIV-infected children might have been missed. The ongoing implementation of early infant diagnosis using DNA polymerase chain reaction and the family

cantered program are expected to increase enrolment of children into ART.

A great achievement was observed through the relatively high percentages of patients received HIV-test at Outpatient unit, Tuberculosis unit and some from the inpatient unit of the health centre. These findings signify the implementation of provider-initiated testing and counselling (PITC) a complement to VCT. PITC was initiated with the aim of increasing uptake of HIV testing, improve access to health services for people living with HIV, and create new opportunities for HIV prevention at the time when Chalinze town had only one stand alone VCT centre. PITC is implemented using the Opt-out approach (WHO 2007) involving the health care provider specifically recommending an HIV-test to patients attended at any of the health centres' units. Then pre-test information is provided, followed by HIV test performed in the usual way unless the patient declines to be tested.

Many studies have recorded high mortality rates in the first three months in patients who were initiated on ART with CD4<200/µl (Jerene et al. 2006). In contrast none of the patients on ART died during the study period, despite of the majority started ART with CD4<200/µl. The possible explanation on the lack of early mortality can be due to the lower prevalence of severe anaemia in this population (mean haemoglobin 10.9 in ART patients). Severe anaemia (Haemoglobin <8g/dl) is known to be correlated with high mortality rates in AIDS patients (Langford et al. 2007).

In this study setting WHO clinical staging was expected to be used more frequently than CD4+T cell count in deciding ART initiation. However, due to unsatisfactory history taking and physical examination practices, clinicians had to wait for CD4+T cell counts results and delayed to initiate patients on ART. Such delays might have contributed to the deaths of patients on care.

Papular Pruritic eruptions (PPE) were the most frequently diagnosed AIDS defining illness in this population. Dermatological manifestations remain a major issue for those living with HIV disease because skin manifestations are often disfiguring and stigmatizing. The characteristic of skin problems in HIV-infected individuals clearly indicates immunosuppression and have accompanied AIDS from early days of the epidemic (Piot et al. 1984), (WHO 1987). PPE is a cutaneous marker of advanced HIV-infection and is known to be uncommon in immune-competent persons (Resneck Jr et al. 2004), (Eisman 2006). Kaposi's sarcoma and Herpes zoster are companions of skin problems in AIDS patients. Although, these disease conditions occur in low frequencies but are always present in HIV-patient cohorts and are associated with severe immunodeficiency (Goedert et al. 1998). Early detection and treatment have been associated with long term survival of patients (Eisman 2006). Thus strategies aimed at active case finding of Kaposi's sarcoma and PPE need to be developed and clinicians should be alert in assessment and initiation of interventions for these problems.

Tuberculosis remains common ADIs in HIV and AIDS patients, and is an early Opportunistic disease in the course of HIV-infection which carries the highest case fatality rate (Dye et al. 1999) (Corbett et al. 2003). At Chalinze health centre Tuberculosis diagnosis rely entirely on clinical suspicion and sputum examination, but still more than 30% of ADIs cases were due to Tuberculosis. This finding indicates that more tuberculosis cases can be diagnosed in this population if standardized Tuberculosis screening tools and chest x-ray examination are added to the sputum microscopy examination. Intensified case detection and contact tracing need to be instituted in tandem with community based prevention measures.

The potential limitations of this study include the fact that patients were not interviewed to solicit their views on the quality of care provided.

Despite of the aforementioned limitation, we have highlighted important findings which provide confidence to program managers and clinicians that health centres can provide ART services. In addition Health centre based ART services improves access to many HIV/AIDS patients in rural areas.

In conclusion, the successes and the weaknesses indicated by this study are the lessons learned and are essential references in the course of HIV/AIDS scaling-up process in rural Health centres. Proper linkage and referral network of health centre ART clinics with nearby diagnostic facilities is essential to ensure quality health care in rural settings. Supportive supervision and clinical mentorship could be established simultaneously with the initiation of ART services in health centres.

Competing interest

No competing interests expressed by authors.

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References

Bhengu, B.R. et al., 2009. Symptoms experienced by HIV-infected Individuals on antiretroviral therapy in KwaZulu-Natal, South Africa. *Applied Nursing Research*.

Corbett, E.L. et al., 2003. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Archives of internal medicine*, 163(9), 1009.

Dye, C. et al., 1999. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. *Jama*, 282(7), 677.

Eisman, S., 2006. Pruritic papular eruption in HIV. *Dermatologic clinics*, 24(4), 449–457.

Gilson, L., Kitange, H. & Teuscher, T., 1993. Assessment of process quality in Tanzanian primary care. *Health Policy*, 26(2), 119–139.

Goedert, J. et al., Spectrum of AIDS-associated malignant disorders. *spectrum*, 1, 2.

Hardon, A.P. et al., 2007. Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa. *AIDS care*, 19(5), 658–665.

Jerene, D. et al., 2006. Predictors of early death in a cohort of Ethiopian patients treated with HAART. *BMC Infectious Diseases*, 6(1), 136.

Katabira, E.T. & Oelrichs, R.B., 2007. Scaling up antiretroviral treatment in resource-limited settings: successes and challenges. *AIDS*, 21, S5.

Katabira, E.T. & Oelrichs, R.B., 2007. Scaling up antiretroviral treatment in resource-limited settings: successes and challenges. *AIDS*, 21(Suppl 4), S5-S10.

Kober, K. & Van Damme, W., 2004. Scaling up access to antiretroviral treatment in southern Africa: who will do the job? *The Lancet*, 364(9428), 103–107.

Langford, S.E., Ananworanich, J. & Cooper, D.A., 2007. Predictors of disease progression in HIV infection: a review. *AIDS research and therapy*, 4(1), 11.

Lyamuya, E. et al., 1996. Performance of a modified HIV-1 p24 antigen assay for early diagnosis of HIV-1 infection in infants and prediction of mother-to-infant transmission of HIV-1 in Dar es Salaam, Tanzania. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 12(4), 421.

Ministry of Health Tanzania (2005), National guidelines for the clinical management of HIV and AIDS, second edition April 2005.

Morrison, J.S., 2002. Expanding antiretroviral treatment in developing countries creates critical new challenges. *Centre for strategic and international studies HIV/AIDS task force report*.

Nsimba, S.E. et al., 2002. Case management of malaria in under-fives at primary health care facilities in a Tanzanian district. *Tropical medicine & international health*, 7(3), 201–209.

Piot, P. et al., 1984. Acquired immunodeficiency syndrome in a heterosexual population in Zaire. *The Lancet*, 324(8394), 65–69.

Posse, M. et al., 2008. Barriers to access to antiretroviral treatment in developing countries: a review. *Tropical Medicine & International Health*, 13(7), 904-913.

Resneck Jr, J.S. et al., 2004. Etiology of pruritic papular eruption with HIV infection in Uganda. *JAMA*, 292(21), 2614.

Sukati, N.A. et al., 2005. HIV/AIDS symptom management in Southern Africa. *Journal of pain and symptom management*, 29(2), 185–192.

Ministry of Health Tanzania (2005), National guidelines for the clinical management of HIV and AIDS, second edition April 2005.

Urassa, M. et al., 2001. The impact of HIV/AIDS on mortality and household mobility in rural Tanzania. *Aids*, 15(15), 2017.

Van Damme, W., Kober, K. & Laga, M., 2006. The real challenges for scaling up ART in sub-Saharan Africa. *Aids*, 20(5), 653.

World Health Organization (1987), Acquired Immunodeficiency Syndrome (AIDS), 1987 revision of CDC/ WHO case definition of AIDS. Wkly Epidedemiol Rec 1988;634-7

World health Organization (2007), HIV/AIDS programme strengthening health services to fight HIV/AIDS 2007, Guidance on provider-initiated HIV testing and counseling in Health facilities.

Wyss, K., 2004. An approach to classifying human resources constraints to attaining health-related Millennium Development Goals. *Human Resources for Health*, 2(11), 6.

Table 8. 2: Characteristics of HIV patients enrolled for ART services between May 2007 and June 2009 at Chalinze Health Centre

Characteristics	All patients (N=895)	CARE patients (N=611)	ART-patients (N=284)
Age group (years) n (%)			
≤24	133(14.8)	98 (16.0)	35 (12.3)
25-34	305(34.1)	212 (34.7)	93(32.8)
35-45	315(35.2)	208 (34.0)	107(37.8)
>45	142(15.8)	93 (15.2)	49(17.2)
Sex n (%)			
Female	622(69.5)	433(70.8)	189(66.4)
Male	273(30.5)	178 (29.2)	95(33.6)
Weight, mean(SD) kg			
Female	46.3(1.5)	49.2(1.2)	43.6 (1.5)
Male	53.3(4.5)	51.4(1.3)	45.1 (1.8)
Functional status n (%)			
Working	605(67.6)	424(69.4)	181(63.9)
Ambulatory	281(31.4)	187(30.6)	94 (33.2)
CD4+T Lymphocytes			
≤350/µl	550(61.5)	324(53.1)	226(79.6)
>350/µl	345(38.5)	287 (46.9)	58 (20.4)
WHO clinical stage			
I& II	364(40.7)	291(47.6)	73(25.7)
III& IV	531(59.3)	320(52.4)	211(74.3)
Hemoglobin, mean(SD)	10.9(2.8)	10.8 (2.7)	10.9 (2.9)
Mortality rate per100 patient-years (95%CI)		2.13 (1.31-3.48)	0.04 (0.01-1.01)

Table 8. 3: Clinical manifestations by CD4+T-Lymphocyte counts of 895 patients with HIV and AIDS attended between May 2007 and June 2009 at Chalinze Health Centre

Clinical feature	CD4+T-Lymphocytes counts			
	<100(N=361) N (%)	100-200(N=227) N (%)	>200(N=307) N (%)	P value
Weight loss	155(42.9)	63(27.9)	74(24.1)	<0.001
Skin itching/rashes	114(31.5)	59(25.8)	58(18.8)	0.001
Fever	107(29.6)	45(19.9)	58(18.8)	0.002
Body weakness	101(28.0)	41(18.2)	42(13.8)	<0.001
Productive cough	93(25.8)	34(14.8)	45(14.8)	<0.001
Headache	75(20.7)	29(12.6)	29(9.6)	<0.001
Numbness	69(19.0)	39(17.1)	43(14.1)	0.212
Nausea and vomiting	40(11.1)	13(5.7)	14(4.7)	0.003
Dry cough	43(11.8)	26(11.3)	23(7.5)	0.137
Parotid enlargement	37(10.2)	22(9.9)	22(7.3)	0.356
Chronic diarrhoea	28(7.8)	9(3.8)	10(3.4)	0.021
Dysphagia	25(7.0)	6(2.8)	13(4.2)	0.052
Abdominal pain	68(18.9)	23(10.2)	14(4.7)	<0.001
Oral Candidiasis	61(16.9)	16(6.9)	16(5.1)	<0.001
Pallor	42(11.7)	6(2.8)	10(3.2)	<0.001
Dermatitis	19(5.3)	10(4.4)	7(2.2)	0.139
Genital discharge	17(4.6)	6(2.8)	5(1.7)	0.066

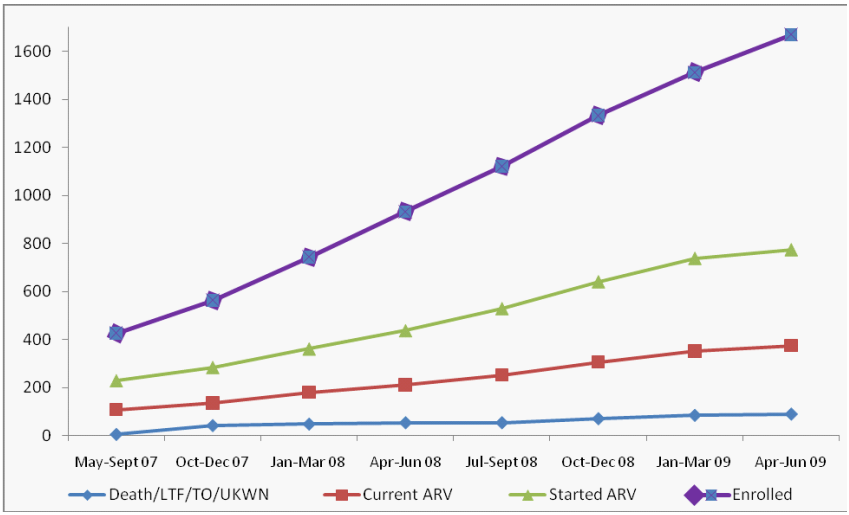

Figure 8.2 : Cumulative number of patients enrolled, started ARV, still on ARV and retention status during the study period (May 2007 – June 2009)

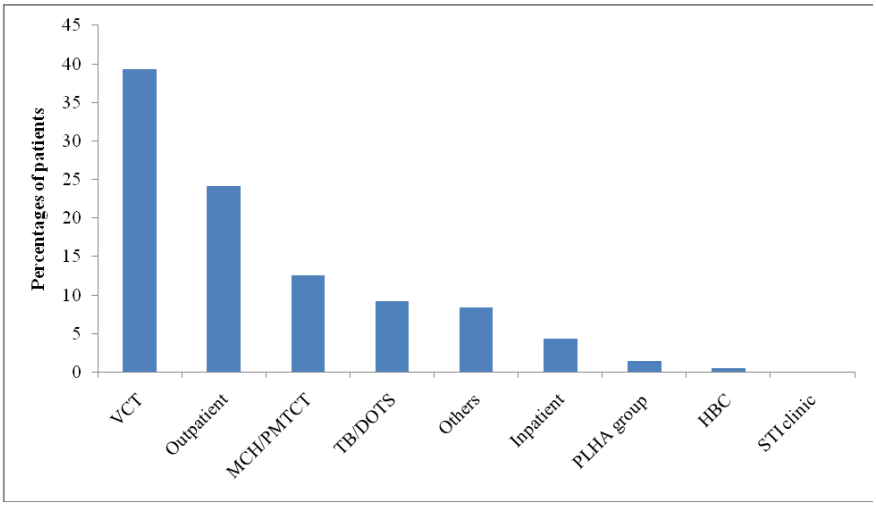

Figure 8.3: Place of HIV test for patients enrolled for HIV care and treatment at Chalinze Health Centre, Tanzania

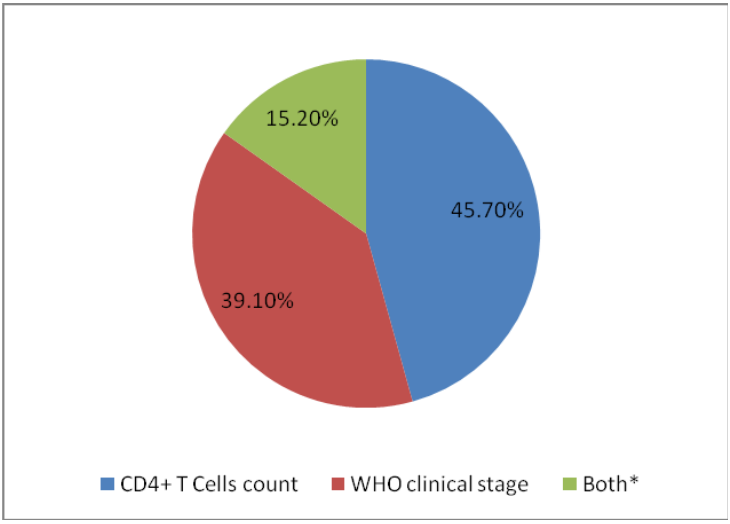

Figure 8.4: Methods used to evaluate patients eligibility to start ART at Chalinze Health Centre, Tanzania

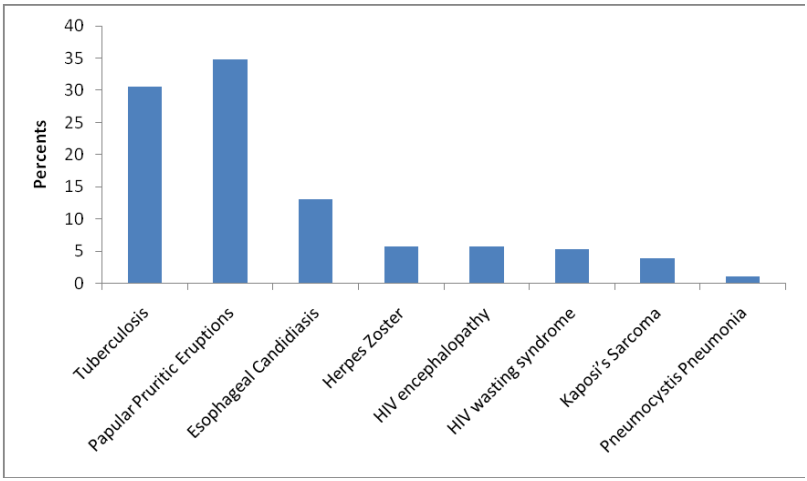

Figure 8.5: AIDS-defining illnesses treated between May 2007 and June 2009 at Chalinze Health Centre, Tanzania (n=282)

Part IV

Discussion, Conclusions and Recommendations

Chapter 9: Discussion, conclusions and recommendations

Management of HIV and AIDS cases remains a challenge for health care workers and program implementers due to heterogeneity of clinical manifestations, concurrent infections and co-morbidity caused by endemic diseases. Over the past decades, management of HIV and AIDS has advanced in various fields ranging from development and testing of pre-ARVs resistance markers in HIV-drug naïve patients, CD4+ T lymphocytes monitoring to the use of fixed dose ARVs combination therapy. Nevertheless, HIV and AIDS continue to be one of the leading causes of morbidity and mortality in SSA (1). Finding effective HIV cure remains the greatest hope for PLHA.

Under the current circumstances and on the absence of an effective cure provision of optimum HIV care and treatment is the only option to prolong lives of PLHA and prevent further HIV infection. More important ART is becoming available in the peripheral (rural) settings where access to heal th services and proper medication is limited. In these settings, until recently HIV related deaths were common due to poor access to ART (2). Gradually, rural residents have started to experience benefits of ART after the establishment of care and treatment services at some health centres.

In poor resourced countries the public health sector have recorded remarkable benefits in patients' survival outcomes due to availability of free ART compared to the period without ART (3). Despite of these achievements higher mortality rates in the first 6 months of ART compared to developed countries has raised concerns. It is possible that early higher mortality is caused by co-infections that lead to continuous co-morbidity coupled with late presentation to care and treatment. The high burden of Opportunistic infections and polyparasitism in poor tropical populations profoundly affects the outcome of HIV/AIDS (4). Co-

infections with unrelated parasites increase the parasites overall virulence and adversely affects the natural history and progression of HIV/AIDS. It has become increasingly clear that HIV/AIDS, tuberculosis, and malaria occur predominantly in populations who are poly-parasitized. Helminths are the most common parasites found in HIV-1, tuberculosis, and malaria infected populations. Almost all of the major tropical diseases have been linked with HIV/AIDS, tuberculosis, and malaria. Several studies point to the increasing risk and severity of clinical malaria that result from helminths co-infection and or Schistosome infections in HIV-1. In Malawi, a study showed that women infected with hookworms were at 1.8 more times higher risk of having malaria than uninfected women (5). Gallagher et al. 2004 observed increased risk of mother-to-child HIV transmission in pregnant women with helminths co-infection (6). In addition, there is some evidence that helminths infections adversely affect the outcome of pulmonary tuberculosis or the progression to active tuberculosis in HIV-1 infected persons. Taken together, this evidence indicates that co-infection with one or more parasites or Opportunistic infections may profoundly affect the outcome of HIV/AIDS, tuberculosis, and malaria.

We are still in the early stages of appreciating the full extent of the co-morbidity that occurs when helminths are superimposed on HIV/AIDS, tuberculosis, and malaria. Anaemia has been revealed as perhaps the most important of the leading co-morbidity conditions. HIV/AIDS, tuberculosis, helminths and malaria infections results in Anaemia, with malaria responsible for the greatest burden. Severe Anaemia resulting from helminths poly-parasitism and malaria produces several adverse health consequences among the three particularly important African subpopulations: pregnant women, children, and individuals with HIV-1 infection. Among individuals with HIV-1 infection, Anaemia has been shown to be an independent risk factor for early death; correction of Anaemia results on decreased risk.

Evidence of the extensive geographic overlap between HIV-1 infection and tropical diseases, together with the deleterious interactions between both groups of infections, suggests significant, new opportunities to reduce the burden of disease in sub-Saharan Africa. HIV/AIDS, tuberculosis, and malaria programs should therefore expand their portfolios to integrate helminths and other neglected tropical disease control to reduce morbidity and mortality in vulnerable populations.

Our study identified about 30% of HIV-infected patients who could not be clinically staged appropriate according to WHO clinical stages, because they lacked the required signs and symptoms required in the guidelines. Some of these patients were found to have CD4+Tcells<200/µl the critical cutoff point below which serious Opportunistic infections occurs. Despite the recent change in criteria for ART initiation in resource limited settings from the previous CD4+Tcells<200/µl to CD4+Tcellsd" 350/µl (7), the challenge of access to CD4 count remains unresolved in peripheral (rural) HIV/AIDS clinics. Clinicians caring for HIV and AIDS patients in the peripheral (rural) are not able to decide on the appropriate management for some patients. Although the WHO clinical criteria continues to be emphasized as the basis for deciding initiation of ART, patients presenting with clinical stages 1 and 2 can easily be regarded as early presenters due to increased awareness of ART benefits and availability rather than an outcome of a changed manifestation of a severe disease which requires further laboratory investigations, which remains un accessible. Patients with Herpes zoster and Papular Pruritic eruptions which are clinical stage 2 conditions were found to have CD4+Tcells<200/µl. Again, promotion of CD4 testing to all patients is a practical approach which is not absolutely feasible in peripheral (rural) settings where blood samples need to be transported for CD4 testing. However, cohort specific clinical manifestation profiles linked to CD4 count levels can complement

decision on when to start ART in patients with symptoms not in fitting with WHO clinical staging listed conditions.

Clinical staging is intended to guide decisions on when to start ART and when to start cotrimoxazole prophylaxis. HIV/AIDS treatment guidelines provide details of specific staging conditions and criteria for recognizing them. Clinicians need to understand and know how to apply these criteria to individual patients. However, our findings at Chalinze health centre cast doubt on the ability of some clinicians to appropriately clinically stage patients. The brief clinical consultations which were not long enough to register complete history and clinical examination raises questions on quality of case management in similar settings. Thus CD4+Tcells count results become an important factor to appropriately manage the patient and avoid delaying ART to patients in need. Introduction of job aids and simplified protocols based on local experiences can improve the overall performance of clinicians and better care of HIV/AIDS patients. Most patients who reported at the clinics during the study period (April 2008 to March 2009) had severe immunosuppression this is indicated by their low median CD4 cell count at presentation (84 cells/µl (IQR 29-127)). This can be explained by late presentation at the beginning of the program a characteristic of most HIV/AIDS programs in SSA. It is expected that as ART services continue to be widely accessible, patients will start to present early to HIV-clinics and reduce losses to follow-up. Several other reasons explain why patients are lost to follow up and present late to clinics. Availability of alternative care provided by local traditional healers partly contribute to treatment delaying patients to seek modern health care, no-adherent and dropout of patients from care (8). It is a common experience in resource poor settings of Africa for HIV-patients to consult traditional healers for psychosocial and health care first before moving to hospital and or other patients move away from hospitals to tradition healers. Collaboration and integration of traditional

healers in HIV and AIDS care programs have benefited patients and the program in some settings of East Africa (9). We recommend establishment of collaboration between traditional healers and HIV program in areas where the two services exist. Traditional healers need training to understand basic HIV/AIDS information including availability and benefits ART. They should be encouraged to refer patients to hospitals and avoid concomitant administration of herbal medicines and ART.

Main findings and their implications for future research and interventions

This study covered four important issues as outlined in the goal and objectives. These findings provide useful considerations in the process of scaling-up and provision of ART in peripheral (rural) or semi-urban settings with limited resources.

With respect to the first objective, the study documented and analyzed HIV and AIDS clinical manifestations and CD4+T lymphocytes count, examined the sensitivity of each symptom or sign to predict CD4+T lymphocytes count d”350 /µl. One key finding is that by combining three symptoms including diarrhoea which persisted for more than two weeks in a HIV-positive individual is a good predictor of CD4+T lymphocytes count d”350 /µl. Considering this finding and the fact that more than 50% of the patients present to HIV and AIDS clinics with CD4+T lymphocytes count d”200/µl, this has significant consequences not only on mortality as described in other studies, but also in the approach to case management. In settings where CD4+T lymphocytes counts are not readily available, local experiences of prevalence and types of symptoms presented by those living with HIV/AIDS should be used to initiate ART. Operation research to document cohort specific HIV clinical presentation correlated to CD4 count levels should be undertaken in all clinics with large numbers of patients.

Some signs and symptoms experienced by HIV and AIDS patients occur across the trajectory of HIV-disease did not efficiently predict CD4+T lymphocytes decline. Such manifestations include: headache, fatigue, abdominal pain and peripheral neuropathy. These symptoms were found relatively weak in predicting severe immunosuppression. It is also important to note however that such symptoms may occur secondary to traditional herbal medications taken by patients prior to enrolment to HIV-clinic and can influence the relationship between symptoms presented and CD4+T lymphocytes changes (10). Each symptom experienced by HIV and AIDS patients influences on the patient's quality of life. Persistent headache is bothersome and may signify an underlying serious systemic condition or co-medications. Skin lesions cause disfiguring and at times serious discomfort due to itching, as a result self stigma, isolation and depression. However, most of these symptoms can be controlled by using ART if initiated during the early stages of AIDS.

HIV clinical manifestations most often mimic clinical symptoms and signs of endemic diseases common in a particular region (11). Bacterial infections including tuberculosis in HIV-infected individuals have been well studied because of their public health importance in most regions of the world (12). Parasites co-infection in HIV/AIDS on the other hand, have currently been given due attention, especially intestinal helminths which present without specific signs and symptoms. However, further research on the role of helminths and other endemic parasites comorbidity in addition to HIV disease and the impact of comorbidity on overall HIV and AIDS case management should also be explored.

With regard to the second part of the first objective, the study investigated the interaction between parasites and HIV in terms of effects on CD4+T lymphocytes and clinical monitoring of HIV/AIDS patients. Current clinical practice in HIV/AIDS clinics do not routinely screen for parasites co-infection in HIV-patients.

Such practices allow underlying morbidity caused by parasites to advance and complicate clinical outcome.

Findings of this study suggest that there is a high prevalence rate of malaria and intestinal worms in HIV/AIDS patients. This should form the bases for cohort specific studies to determine the burden of parasites co-infection in HIV/AIDS patients and choose the appropriate modality of care. Similarly, HIV/AIDS clinics should be seen as opportunity for implementing intervention studies to address the problem of co-infection and co-morbidity. Study results show the benefits of treating parasites at the time of initiating ART through improved CD4+T lymphocytes counts recovery equivalent to that of patients without parasites co-infection. It can be argued that if HIV/AIDS programs can implement mass treatment for endemic parasites at care and treatment clinics, recurrent morbidity and probably mortality can be further reduced. It is important, therefore, to conduct research to establish local burden of parasites in HIV-infected patients' cohorts in order to guide interventions.

The second objective of this study examined factors related of non-adherence to combination ART. Optimal ART adherence is essential for maximal suppression of viral replication and long term survival of patients. Different settings have specific barriers that influence adherence to ART; such barriers are not necessarily shared by populations in other settings. This study identified two behavioural factors: disclosure status and alcohol drinking as strong predictors of non adherence to ART. Other non-behavioural factors were inadequate knowledge of basic prevention methods; poor adherence to clinic appointments (because of lack of money for transport) and unsatisfactory with providers. Study findings clarify the dynamic nature of adherence to ART and its dependence on setting-specific influencing factors. Adherence improvement strategies need to take into consideration site specific determinants, patient experiences and concerns. It is even more complex to maintain adequate

adherence in rural areas due to seasonality of economic activities and consequential seasonal household mobility especially in settings where farms are located far away from homes and in transhumance nomadic populations (13).

There are several strategic options for Tanzania National AIDS Control Program to consider implementing or adopting for peripheral (rural) population. In the case of seasonal or transhumance population migrants to farm lands quarterly mobile ART clinics to selected farm sites could provide an opportunity to maintain adherence to ART. For non mobile population, patients residing far from the HIV/AIDS clinic quarterly ARVs prescriptions and or drug refills collected by a treatment assistant can reduce transport costs and encourage adherence success. Nevertheless, research is needed on ART adherence and virological suppression in patients receiving three monthly ARVs supplies. The Tanzania National AIDS Control Program in collaboration with district ART teams need to identify mobile populations and establish community-directed outreach ART clinical teams. Such teams can be deployed in a regular basis to sites far from ART clinics. This strategy will ensure continued access to ART and improve adherence for patients in mobile population. For peripheral (rural) hard to reach population establishing ART refill stations within the community could be considered and will benefit inhabitants of these areas.

HIV/AIDS care and treatment clinic provides an opportunity to deliver prevention messages and interventions to patients. Usually patients establish trusted relationship with health care providers and hence are more likely to listen, accept and practice prevention methods provided by health care workers. The study finding show that patient with inadequate knowledge of basic prevention methods were more likely to be non-adherent to ART. This finding is striking and can be extrapolated to the deficiency in contents of health talks. Health talks are useful in terms of HIV-infection control if delivered properly and contain relevant

information. AIDS prevention messages constitute part of post HIV-test counselling and continuous health education delivered to patients during routine consultations. It was therefore expected that patients would be knowledgeable of prevention messages but there was no compelling evidence found.

The quality of provider-patient interaction is an important factor in determining patient satisfaction with the services provided, and responsible for poor access to services. Stress of the work environment creates a negative impact on the provider behaviour. Sometimes health providers become irritable and handle patients in the wrong way because of infrastructure problems (patient overcrowding, lack of electricity and inadequate water supply). Overwork due to staff shortages which lead to performing of multiple tasks; and shortages of drugs and supplies (14) negatively impact on provider-patient relationship. The use of non-professional staff to perform some activities which do not require much of a medical knowledge (15), optimizes skills of the health worker to cope with growing patient loads. Regular supportive supervision, opportunities for professional and career development, and recognition of staff performance boost staff morale, and job satisfaction (16).

The third objective of this study focused on experiences and lessons learned in the process of providing ART in peripheral (rural) health centre. The process of scaling-up ART is seen as a comprehensive and equitable strategy to stem the burden of HIV/AIDS in poor rural settings. However, the use of ART in poor settings has been challenged mainly due to lack of adequate infrastructure and the related medication costs (17). These issues have been continuously addressed by the International community, but the widespread use of ART raises the issue of lack of experience and best model of care to be replicated in similar settings.

The following lessons derived from managing HIV and AIDS at the Chalinze health centre ART services outcomes to date and the possibility of replication of similar achievements to other settings, the following aspects stand out: (1) ART services can be provided effectively at a Health centre by less trained medical staff after a two weeks training course in HIV and AIDS care and treatment. (2) Proximity of ART services encourages entry and retention in care for patients who initially could not afford regular travelling to access care and treatment services. (3) Providing ART services at Health centre strengthens the primary health care system and it also provides the opportunity to benefit none HIV health care services in terms of infrastructure improvement, improved laboratory diagnostics and strengthened referral networks.

The concept of integrated HIV/AIDS care and treatment as pioneered in Tanzania by the St.Francis Designated District Hospital chronic disease clinic (18) has benefits beyond improving health care system. At Chalinze health centre, the integrated nature of ART services gives an opportunity to patients to receive all appropriate essential services in a coordinated way. The dramatic physical wellbeing of AIDS patients who were at a terminal stage and reduction in morbidity as a result of ART intake increased confidence in clinical care. As result, the multi-purpose structure of health centres services creates an environment that enables HIV/AIDS patients to be accepted by their communities where they live. Under this clinical arrangement, the role of ART in reducing stigma and discrimination for PLHA can be realized. Furthermore, HIV and AIDS require multi-drug therapy over an extended period of time so providing ART at health centres close to majority of the poor patients promises good treatment adherence and reduction of risk factors for development of drug resistance (19)]. Under these circumstances and the benefits observed, it is possible to provide ART safely and effectively in a resource poor setting.

Recommendations

The findings of this study provide useful recommendations for HIV/AIDS program, health system and the community.

HIV/AIDS program level

(i) Introduction of additional screening tools for pneumonia and Kaposi's sarcoma

Pneumonia and Kaposi's sarcoma requires x-rays and skin biopsy for diagnosis confirmation, respectively. The lack of these diagnostic technologies in rural health facilities results in missed diagnosis and occasionally suspected cases of these conditions receives referral at patients' own transport costs. Many patients in this study presented with chronic cough and fever, while the number of patients diagnosed with pneumonia was too low compared to the number of cough cases attended. Similarly Kaposi's sarcoma lesions can be easily missed by clinicians during clinical examination, especially lesions in the mouth and other body cavities. Development of symptom and signs based screening tools similar to the one used for screening tuberculosis will increase case detection and provision of appropriate management. Additionally, symptom and signs checklist tools if used properly are likely to improve the quality of HIV-case management in peripheral (rural) health centres.

(ii) Integrated supportive supervision

The goal of supportive supervision is to promote effective, efficient and equitable health care.

Providers in health centres require regular supervision from supervisors who can provide clear guidance and sufficient information aimed at improving patient management

procedures, provider-patient interactions and overall management of primary health care facilities.

HIV and AIDS programs need to develop an intervention package containing all components of ART services. The intervention package will then be used by Regional health managers during routine supervision.

(iii) Clinical mentorship program

Periodic mentorship program for clinical staff need to be instituted to enhance the knowledge and clinical decision making skills of clinicians providing care to HIV and AIDS patients. A multi disciplinary team of trainers drawn from the region health management team equipped with skills to provide one-on-one and small group case based training need to be established. Such an intervention will improve the quality of HIV case management and clinical outcomes.

Health care delivery system level

(i) Task shifting

Task shifting must be seen as part of an overall strategy that includes tangible measures to increase, retain and sustain existing and new cadres of staff. Existing staff need to be flexible, motivated and support the delegation of some of their duties in order to cope with the increasing burden of HIV/ AIDS. Examples of tasks which can be lay-health care at a health centre level include: provision of basic HIV support, treatment adherence and psychosocial support; record clerks filling in basic patient information and measuring body weight.

(ii) Staff shortages

Addressing staff shortages through expanded training opportunities and incentives to attract health care workers to remain and or accept to move and work in peripheral (rural) health centres is an important step towards ensuring quality health services. The use of retired health care workers to provide less demanding services like antenatal care and vaccination should be encouraged to alleviate work load to existing staff.

(iii) Laboratory diagnosis

Strengthening laboratory infrastructure at health centres requires the provision of basic equipments and training of technicians to improve their knowledge and skills and provide quality results. Basic laboratory tests that are essential for routine care like stool examination for helminths, urine, sputum, haemoglobin and blood slides need to be improved at the Regional hospital and health centres. This should be carried out in tandem with the establishment of quality assurance systems and refresher training of laboratory technicians. Sample transportation from health centre to regional laboratories for CD4 cells count analysis, results turnaround time and reliability of the results need improvement. Coordination and communication between laboratories, clinic units and patients, equipment maintenance and referral processes should be established.

(iv) Routine screening of helminths in stool and urine; and malaria parasites in blood. Patients registering for the first time at care and treatment clinics should be screened for parasites prevalent in the area. Tanzania National AIDS Control Program need to incorporate parasites screening and treatment in the HIV/AIDS case management guidelines and treatment packages.

(v) Changing HIV/AIDS clinical presentation

Tanzania National AIDS Control Program in collaboration with clinics managing large HIV/AIDS cohorts need to regularly review HIV/AIDS clinical presentation and their utility in WHO clinical staging. This approach will assist clinicians in peripheral (Rural) settings to improve patient management and reduce possibility of inappropriate clinical staging. In addition data will readily available for revision of National treatment guidelines.

(vi) Availability of simpler CD4+T lymphocytes counts

Development of simpler CD4+T lymphocytes counts testing tools which uses solar power and requires no electricity and or refrigeration (cold chain).

HIV/AIDS patients' management continues to be guided primarily by clinical staging owing to the insufficient availability (or frequent breakdowns) of CD4 cells count machines, shortage of qualified medical staff and lack of laboratory reagents due to logistic issues. CD4+T lymphocytes count machines currently in use are very complex and require highly qualified laboratory technicians to operate. These equipments cannot be installed in peripheral (rural) health centre with simple infrastructure and unreliable electricity supply.

Given all these technical and logistic issues, we propose the development of a simple and user friendly CD4+T lymphocytes count instrument which can be used in peripheral (rural) health facilities. The instrument should mimic the pregnancy test or the HIV-antibody testing instruments used in Voluntary Counselling and Testing. A two compartment instrument with different colour coding for each compartment categorized by the amount of CD4+T lymphocytes concentration (CD4d" 350 cells/µl and

CD4>350 cells/µl to provide useful information to guide HIV/AIDS clinical care.

(vii) Improved (IEC) information

Although IEC materials are available in health facilities the need to improve information contents of these materials to cover patients' needs and concerns is critical. Patients need to be educated on ART benefits, adherence requirements and eligibility to ART. The amount of information should be reduced and simplified to enhance easy recall.

(viii) Poor quality of services provided

Quality of care is a concern in health care facilities (20) and both technical and perceived quality of care needs to be addressed through improved appropriateness of diagnosis, prescribed treatment and interpersonal care including proper advice. Intervention to improve quality of care should consider addressing staff motivation, improved counselling and patients' follow-up.

(ix) Sub-optimal adherence to ART in mobile population

NACP and District HIV/AIDS programs collaboratively can develop and implement adherence strategies to address adherence problems affecting patients residing in mobile or migratory populations.

Community level

i) Advocacy

Community based advocacy of the benefits of ART and early clinical consultation after a HIV-test positive result is required to reduce the number of late reporting and poor adherence to

ART. In principle health intervention programs should incorporate ART information with emphasis to access, benefits and adherence requirements. This strategy will enhance early and appropriate treatment seeking behaviour.

ii) ART refill stations

Geographic access to health facilities is relatively good in Tanzania with approximately 75% of the population living within 5 km of a health centre or dispensary (21). Since not all health centres have the capacity to provide full range ART services. However, they provide an important infrastructure which could be used to improve access to ART in peripheral (rural) areas by establishing ART refill stations. The dispensary provides good infrastructure for storage of drugs and monitoring of adherence to ART. Since the dispensary is within walking distances for most of the people in peripheral (rural) settings transport costs and waiting times is reduced.

Implications for future research

1. Case-control studies are needed in peripheral (rural) and urban settings to determine factors contributing to delay for seeking ART care after testing HIV-positive. This study indicated substantial delay in seeking care following a HIV-test positive result. The consequences of delayed initiation of care and treatment are determinants to patient survival, ART effectiveness and HIV-1 transmission.

2. Cohort studies are required to determine the levels of adherence to ART and virological suppression for patients receiving three months ART supplies. The comparison group may be patients receiving routine monthly ART supply.

3. HIV/AIDS Cohort specific studies on the types and burden of parasites and other important co-infections will be used to guide development of site specific intervention strategies and case management approaches.

4. Cross-sectional studies specific to a geographical area and HIV/AIDS cohort are need to establish HIV/AIDS patients' cohort specific clinical manifestations. These studies will provide evidence for continuous amendments of care and treatment guidelines.

References

1. Brinkhof MWG, Boulle A, Weigel R, Messou E, Mathers C, Orrell C, et al. Mortality of HIV-Infected Patients Starting Antiretroviral Therapy in Sub-Saharan Africa: Comparison with HIV-Unrelated Mortality. PLoS Med. 2009 Apr;6(4).

2. Lawn SD, Myer L, Harling G, Orrell C, Bekker L, Wood R. Determinants of Mortality and Losses from an Antiretroviral Treatment Service in South Africa: Implications for Program Evaluation. Clinical Infectious Diseases. 2006;43(6):770-776.

3. Hogan DR, Baltussen R, Hayashi C, Lauer JA, Salomon JA. Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries. BMJ. 2005 Dec 17;331(7530):1431-1437.

4. Martinson NA, Karstaedt A, Venter WF, Omar T, King P, Mbengo T, et al. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. AIDS. 2007 10;21(15):2043-2050.

5. Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P. Malaria and hookworm infections in relation to haemoglobin and serum ferritin levels in pregnancy in Masindi district, western Uganda. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008 Feb;102(2):130-136.

6. Gallagher M, Malhotra I, Mungai PL, Wamachi AN, Kioko JM, Ouma JH, et al. The effects of maternal helminth and malaria infections on mother-to-child HIV transmission. Aids. 2005;19(16):1849.

7. World Health Organization 2010. Antiretroviral Therapy for HIV infection in Adults and Adolescents. Recommendations for a public health approach 2010 revision.
8. Muela HS. Community understanding of malaria, and treatment-seeking behaviour, in a holoendemic area of southern Tanzania. University of Basel.PhD thesis Juni 2000.

9. Green EC. Traditional Healers and AIDS in Uganda. The Journal of Alternative and Complementary Medicine. 2000 2;6(1):1-2.

10. Mills E, Cooper C, Seely D, Kanfer I. African herbal medicines in the treatment of HIV: Hypoxis and Sutherlandia. An overview of evidence and pharmacology. Nutr J. 2005;4:19.

11. Karp CL, Auwaerter PG. Coinfection with HIV and tropical infectious diseases. II. Helminthic, fungal, bacterial, and viral pathogens. Clin Infect Dis. 2007;45(9):1214-20.

12. Karp CL, Neva FA. Tropical infectious diseases in human immunodeficiency virus-infected patients. Clin Infect Dis. 1999;28(5):947-63; quiz 964-5.

13. Hampshire K. Flexibility in Domestic Organization and Seasonal Migration Among the Fulani of Northern Burkina Faso. Africa. 2006 8;76(3):402-426.

14. Bassett MT, Bijlmakers L, Sanders DM. Professionalism, patient satisfaction and quality of health care: Experience during Zimbabwe's structural adjustment programme. Social Science & Medicine. 1997 Dec;45(12):1845-1852.

15. Callaghan M, Ford N, Schneider H. A systematic review of task- shifting for HIV treatment and care in Africa. Human Resources for Health. 2010;8(1):8.
16. Zachariah R, Ford N, Philips M, S.Lynch, Massaquoi M, Janssens V, et al. Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009 Jun;103(6):549-558.

17. Farmer P, Léandre F, Mukherjee JS, Claude M, Nevil P, Smith-Fawzi MC, et al. Community-based approaches to HIV treatment in resource-poor settings. Lancet. 2001;358(9279):404–409.

18. Stoeckle M, Mchomvu R, Hatz C, Battegay M, Aris EA, Mshinda H, et al. Moving up from 3 by 5. The Lancet Infectious Diseases. 2006 Aug;6(8):460-461.

19. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clinical Infectious Diseases. 2003;37:1112–1118.

20. HERA. District health Services Delivery in Tanzania. Where are we in terms of quantity and quality of health care

provision? Reet, Belgium, Health Research for Action. Annual Health Sector Review 2006.

21. United Republic of Tanzania . Poverty and Human Development Report 2005. United Republic of Tanzania, Research and Analysis Working Group, Dar es Salaam.

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Publications and Presentations

HIV/AIDS clinical manifestations and their implication for patient clinical staging in resource limited settings in Tanzania. (submitted to The Open AIDS Journal, 2010)

Randomized controlled safety and efficacy trial of two vitamin A supplementation schedules in Tanzanian infants. (Am J cli Nutr 2007, 85: 1312-9)

Skin diseases among school children in rural Tanzania and an assessment of therapeutic needs. (Tropical Doctor Journal, Volume 36, Number 4, October 2006, pp.219-221(3))

Challenges of site support for HIV/AIDS care and treatment in Tanzania. (Paper presented at ICAP annual conference, March 2006)

Safety and Efficacy of vitamin A in infants given alongside EPI vaccines. (Presented to IVACG, Annual Conference in Lima, Peru, and WHO headquarters, Vitamin A group, November 2004)

Assessment of quality of malaria care in pregnancy at Mkuranga District Hospital. (MPH Thesis, August 2002)