

**Prevalence and Factors associated with Opportunistic infections in HIV positive patients on Antiretroviral Therapy in Uganda**

**Abstract**

**Introduction**

Opportunistic infections (OIs) remain the single main cause of ill-health and death among HIV/AIDS patients in resource poor countries. We assessed the prevalence of 17 OIs and associated factors among HIV positive patients on highly active antiretroviral therapy (HAART) in Uganda.

**Methods**

Observational data from 2004 to 2013 for adult HIV positive patients ( $\geq 15$  yrs) obtaining care and treatment from the AIDS support organization (TASO) in Uganda were reviewed. Electronic data were obtained from TASO HIV clinics representing 4 different geographical areas of Uganda. Descriptive statistics were summarized in terms of frequencies and percentages. Mantel-Haenszel and logistic regression were used to assess the factors associated with occurrence of OIs.

**Results**

Between 2004 and 2013, a total of 36,133 HIV patients were enrolled on HAART of which two thirds (66%) were female and one third (34%) were male. In univariate analysis, significant differences were observed between male and female ART clients with men being older (median age 36yrs IQR 29-43 vs 32 yrs IQR 26-39,  $p < 0.0001$ ); likely to be more educated ( $>$ secondary 31% vs 19%,  $p < 0.0001$ ); likely to be more severely ill (CD4 count  $< 100$  26% vs 21%,  $p < 0.0001$ ); were more likely to be married (65% vs 42%,  $p < 0.0001$ ) and were more likely to be formally employed (27% vs 12%,  $p < 0.0001$ ). Mean annual prevalence for any OI in 2004 was 57.6% and in 2013 was 27.5% ( $X^2_{trend} = 122$ ,  $b = -0.0283$ ,  $p < 0.0001$ ). The most commonly encountered OIs were geohelminths (35%), diarrhea  $< 1$  month (18%) and mycobacterium tuberculosis (11%). Factors associated with any OI after HAART were male gender, if from Northern Uganda, low education ( $<$ primary), baseline WHO stages III&IV, stavudine ART regimen, baseline CD4 count  $< 100$  cells/ $\mu$ l, low baseline weight  $< 55$  kg and period 2004-2008 ( $p < 0.05$ ).

**Conclusion and recommendations**

In these settings, the burden of OIs is still high in spite of increased access to HAART. The prevalence of geohelminthes and diarrhoea is worrying among HIV patients on HAART. Men remain at greater risk of OIs and should be the main target for early HAART initiation.

**Key words:** HIV/AIDS, Opportunistic infections, Antiretroviral therapy, Prevalence, TASO, Uganda

**Introduction**

Acquired immunodeficiency syndrome (AIDS) is one of the most challenging infectious diseases of the 21<sup>st</sup> century. The disease which currently has no cure is caused by the deadly Human Immunodeficiency Virus (HIV) whose case

fatality rate is well above 95 % in the absence of treatment[1]. According to World Health Organization global HIV/AIDS update report 2013 , 33.4million people worldwide were estimated to be living with the deadly virus by the end of 2013 of which 67% (22.4 million) were in sub-Saharan Africa[2]. Since the outbreak of the HIV pandemic, it is estimated that over 30 million people worldwide have died due to AIDS of which more than 70% were from sub-Saharan Africa[2].

Opportunistic infections (OIs) remain the single main cause of ill-health and death among HIV/AIDS patients in resource poor countries [3-5]. OIs lower the quality of life of HIV infected persons, speeds up the rate of progression to fully blown AIDS, reduces patients' response to antiretroviral treatment especially when co-infected with tuberculosis, increases stigma and limits one's ability to work and are usually associated with high medical care costs [1, 6]. OIs have therefore greatly contributed to poverty among those infected and affected by HIV/AIDS hence an impediment to the attainment of the millennium development goals (MDGs) on health and poverty eradication in resource poor countries.

Although the natural history of AIDS tends to be similar in most patients, the patterns of OIs that largely define the symptomatic and clinical manifestation of AIDS tend to vary in different regions of the world [4, 7, 8] . Thus, while HIV patients in developed countries rarely suffer from bacterial and protozoal infections, they are a major cause of morbidity and mortality in resource-poor countries[4, 8, 9]. However, with increasing availability of Highly Active Antiretroviral Therapy (HAART) and other highly potent prophylactic and therapeutic drugs to eligible HIV patients, the risk of suffering from an opportunistic infection has been substantially reduced[2]. However, HIV positive patients in sub-Saharan Africa have a problem of late enrolment on HAART and adherence problems while on HAART sometimes due to drug side effects thereby increasing the risk of OIs, morbidity and death[10]. HIV positive patients in resource poor settings also suffer because of the high risk of exposure to potential pathogens which are endemic in these settings and most patients suffer from nutritional deficiency resulting in poor prognostic outcomes while on HAART [11]. Universal prophylaxis using Co-trimoxazole also known as Trimethoprim/sulfamethoxazole (TMP-SMX) has also been shown to prevent or significantly reduce the incidence of opportunistic infections and related mortality in HIV-infected individuals [12-15] . In Sub-Saharan Africa where access to HAART is still limited, cotrimoxazole prophylaxis remains the most viable alternative and has greatly increased the chances of survival for HIV-infected individuals who are eligible but cannot access HAART[16]. UNAIDS recommends cotrimoxazole prophylaxis for life to all persons living with HIV/AIDS regardless of their immunological status[17].

In Uganda, adult HIV prevalence stands at 6.7% with an estimated 130,000 new infections annually[18]. HAART roll out in public health facilities is mainly funded by donors such as the Global fund for HIV/AIDS, TB and malaria (GFATM), the presidential emergency programme for AIDs relief (PEPFAR) and the World Bank multi-country HIV/AIDS programme (MAP). By end of 2013, 69.4% (570,373/821,721) of eligible adults and children had access to HAART; though this was still below the 80% national target by 2015 [19]. In 2003, Uganda

introduced universal cotrimoxazole prophylaxis for all HIV infected adults and children regardless of their immunological status and whether they are on HAART or not[20]. In spite of free access to HAART and cotrimoxazole prophylaxis for all who test HIV positive, only 13% of adult women and 11% of adult men ever tested and known their HIV status [21] implying that majority are more likely to present for treatment with advanced HIV disease. In fact previous studies in Uganda have shown 40% of those eligible for HAART present with late disease stage for treatment with increased risk of opportunistic infections and death [22-24]. The purpose of this study was to assess the prevalence of OIs and associated factors among HIV positive patients obtaining care and treatment from TASO ART programme in Uganda in the era of HAART ( 2004 -2013).

## **Methods**

### **2.1 Design**

This was a cross-sectional retrospective review of observation data from 2004 to 2013 for adult HIV positive patients ( $\geq 15$  yrs) obtaining care and treatment from the AIDS support organization (TASO) in Uganda. 17 OIs were studied namely mycobacterium tuberculosis, cryptococcal meningitis, cryptosporidiosis, oral candida, esophageal candida, bacterial pneumonia, confirmed malaria, geohelminthes, kaposi sarcoma, herpes zoster, genital ulcer, toxoplasmosis, herpes simplex labialis, diarrhoea  $< 1$  month, oral hairy leukoplakia, cytomegalovirus and pneumocystis carini/jiroveci pneumonia.

### **2.2. Study Setting**

TASO is one of the oldest and largest HIV/AIDS care and treatment program in Uganda and sub-Saharan Africa. TASO was founded in 1987 and has 11 HIV/AIDS clinics spread across Uganda which have been nationally recognized as centres of excellence (CoE) in HIV/AIDS care and treatment. Patients that are HIV positive are encouraged to register with TASO clinics for care, treatment and social support. The clinics offer comprehensive HIV treatment and care, including provision of free antiretroviral drugs and cotrimoxazole prophylaxis. TASO HAART programme started as part of the National HAART roll-out programme in public health facilities in 2004. Being one of the largest HAART providers in the country, TASO attracted a lot of support from different funders supporting HAART programmes in sub-Saharan Africa including the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Initially, HAART eligibility was based on WHO 2006 guidelines i.e. WHO stage 3 or 4 illness or a CD4 cell count  $< 200$  cells/ $\mu$ l for adults and adolescents and WHO stage III, advanced stage II or stage I with CD4 cell percentage less than 20% for those more than 18 months of age[25]. However, in 2010 new HAART guidelines [26] that raised the threshold for adults and adolescents to a CD4 cell count  $\leq 350$  or WHO clinical stage 3 or 4 irrespective of CD4 cell count were adopted [27]. Those who are not eligible for HAART are offered cotrimoxazole prophylaxis. Additionally TASO has a robust home-based care programme that includes community volunteers/treatment partners that help to monitor HAART adherence, adverse effects, opportunistic infections and reporting those who die. All services are free of charge including anti-retroviral drugs (ARVs) for those who are eligible[28].

### 2.3 Sampling and sample size

Four TASO HIV clinics were purposively selected basing on volume and quality of data and geographical representation. The HIV clinics selected were TASO Mulago HIV clinic in central Uganda, TASO Mbarara HIV clinic in south-western Uganda, TASO Tororo HIV clinic in Eastern Uganda and TASO Gulu HIV clinic in Northern Uganda. All HIV positive adults (15 years and above) who were enrolled on HAART at the selected HIV clinics in the period between 2004 and 2013 were included in the study.

### 2.4 Data collection

TASO medical staff systematically registered the clients' background and medical information following an established protocol for all TASO HIV clinics. In brief, clients were expected to attend the clinic at least once a month. At each clinic visit, data per client was collected on a standardized medical form detailing the client's demographic information, clinical condition, medical history, OI diagnosis, ART use, prophylaxis use, any other treatment given and side effects/toxicities if any. An OI diagnosis criterion is based on WHO and Uganda ministry of Health guidelines [25-27, 29]. Data were then compiled and entered into the TASO electronic data base by TASO data administrator using EPIINFO vs3 in Access format. Relevant data were extracted by the data administrator, delinked from overt identifiers and then handed over for analysis

### 2.5 Data Analysis

The extracted data were analyzed using Stata statistical software version 13.1 (Stata Corp, College station, Texas, USA). Descriptive statistics were by frequencies and percentages. For categorical variables, chi-squared test was used to test for the differences in proportions and Wilcoxon rank-sum test for metric variables. Monthly prevalence was calculated from the total number of cases for any of the 17 OIs divided by the total number that attended the clinic per month. Annual prevalence was calculated from the mean of the monthly prevalences in a year. Only one clinic visit and one episode per OI were considered per person per month. Mantel-Haenszel and logistic regression were used to assess the factors associated with occurrence of OIs and presented the results in terms of crude odds ratios (cORs) and adjusted odds ratios (aORs) with 95% confidence intervals. In multivariate analysis, variables showing significant association in univariate analysis were included in logistic regression to calculate adjusted odds ratios with 95% confidence intervals. All significance tests were two sided with a p-value <0.05 considered significant.

### 2.6 Ethical considerations

The study obtained ethical clearance from Makerere University School of Public Health Higher Degrees Research and Ethics committee and the Uganda National Council for Science and Technology. Since this was retrospective records review the above ethical committees waived off the need for informed consent from study participants. However, written permission was obtained from TASO for conducting the study and publication of findings. All data were handled strictly anonymously and confidentially.

## Results

Baseline information at HAART enrolment and sex segregated are presented in **Table1**. Between 2004 and 2013, a total of 36,133 HIV patients were enrolled on HAART of which two thirds (66%) were female and one third (34%) were male.

**Table1: Characteristics of patients started on HAART between 2004 and 2013**

| Variable                                     | Total cohort | Female      | Male       | p-value |
|----------------------------------------------|--------------|-------------|------------|---------|
| <b>Gender (36,133), n (%)</b>                |              |             |            |         |
| Female                                       | 23,767(66)   | -           | -          | -       |
| Male                                         | 12,366(34)   |             |            |         |
| <b>Median age(36,120), n(IQR)</b>            | 33(27-40)    | 32(26-39)   | 36(29-43)  | <0.0001 |
| <b>Age (36,120), n (%)</b>                   |              |             |            |         |
| <35yrs                                       | 19,338 (54)  | 13,894 (58) | 5,444 (44) | <0.0001 |
| >=35yrs                                      | 16,782 (46)  | 9,863 (42)  | 6,919 (56) |         |
| <b>Location (36,133), n (%)</b>              |              |             |            |         |
| Eastern                                      | 9,793(27)    | 6,271 (26)  | 3,522(28)  | <0.0001 |
| Central                                      | 9,493(26)    | 6,573(28)   | 2,920(24)  |         |
| Western                                      | 8,576(24)    | 5426(23)    | 3150(25)   |         |
| Northern                                     | 8,271(23)    | 5497(23)    | 2774(23)   |         |
| <b>Education (n=34,337), n (%)</b>           |              |             |            |         |
| Primary/none                                 | 26,331(77)   | 18,165(81)  | 8,166(69)  | <0.0001 |
| >=Secondary                                  | 8,006(23)    | 4,342(19)   | 3,664(31)  |         |
| <b>Marital status (n= 34,338), n (%)</b>     |              |             |            |         |
| Single/never married                         | 2148(6)      | 1,260(6)    | 888(7)     | <0.0001 |
| Married                                      | 17187(50)    | 9,523(42)   | 7,664(65)  |         |
| Divorced                                     | 5778(17)     | 4,342(19)   | 1,436(12)  |         |
| Widowed                                      | 6932(20)     | 6,118(27)   | 814(7)     |         |
| others                                       | 2293(7)      | 1,254(6)    | 1,039(9)   |         |
| <b>Occupation (n=33,454), n (%)</b>          |              |             |            |         |
| Paid employee                                | 5,731(17)    | 2,611(12)   | 3,120(27)  | <0.0001 |
| Self employed                                | 12,157(36)   | 9,193(42)   | 2,964(26)  |         |
| Subsistence farmer                           | 13,283(40)   | 8,855(40)   | 4,428(38)  |         |
| others                                       | 2,283(7)     | 1,196(6)    | 1,087(9)   |         |
| <b>WHO clinical stage (n=36, 133), n (%)</b> |              |             |            |         |
| I&II                                         | 16,268(45)   | 10,643(45)  | 5,625(45)  | 0.200   |
| III&IV                                       | 19,865(55)   | 13,124(55)  | 5,625(55)  |         |
| <b>CD4gp (n=22,301), n (%)</b>               |              |             |            |         |
| 0-100                                        | 5,137(23)    | 3,219(21)   | 1,918(26)  | <0.0001 |
| >100                                         | 17,164(77)   | 11,819(79)  | 1,918(74)  |         |
| <b>Weight (23,848), n (%)</b>                |              |             |            |         |
| <55years                                     | 11,853(50)   | 8,156(52)   | 3,697(45)  | <0.0001 |
| >=55years                                    | 11,995(50)   | 7,466(48)   | 3,697(55)  |         |
| <b>Adherence to ART</b>                      |              |             |            |         |
| <=95%                                        | 7,579(21)    | 5,151(22)   | 2,428(20)  | <0.0001 |
| >95%                                         | 28,554(79)   | 18,616(78)  | 2,428(80)  |         |
| <b>ART regimens</b>                          |              |             |            |         |
| Stavudine                                    | 3,926(11)    | 2,743(11)   | 1,183(10)  | <0.0001 |
| Zidovudine                                   | 18,142(50)   | 11,881(50)  | 6,261(50)  |         |
| Tenofovir                                    | 9,931(28)    | 6,397(27)   | 3,534(29)  |         |
| Other                                        | 4,134(11)    | 2,746(12)   | 1,388(11)  |         |
| <b>Year of enrolment on HAART</b>            |              |             |            |         |
| 2004-2008                                    | 12,433(34)   | 8,439(36)   | 3,994(32)  | <0.0001 |
| 2009-2013                                    | 23,700(66)   | 15,328(64)  | 8,372(68)  |         |

In univariate analysis, significant differences were observed between male ART clients and female ART clients with men being older (median age 36yrs IQR 29-43 vs 32 yrs IQR 26-39,  $p<0.0001$ ); likely to be more educated(>secondary 31% vs 19%,  $p<0.0001$ ); likely to be more severely ill(CD4 count<100 26% vs 21%,  $p<0.0001$ ); were more likely to be married(65% vs 42%,  $p<0.0001$ ) and were more likely to be formally employed (27% vs 12%,  $p<0.0001$ ). Generally, a significant decreasing mean annual prevalence trend was observed for any OI reducing from 57.6% in 2004 to 27.5% in 2013 ( $X^2_{trend} = 122$ ,  $b = -0.0283$ ,  $p < 0.0001$ ) (Figure 1).

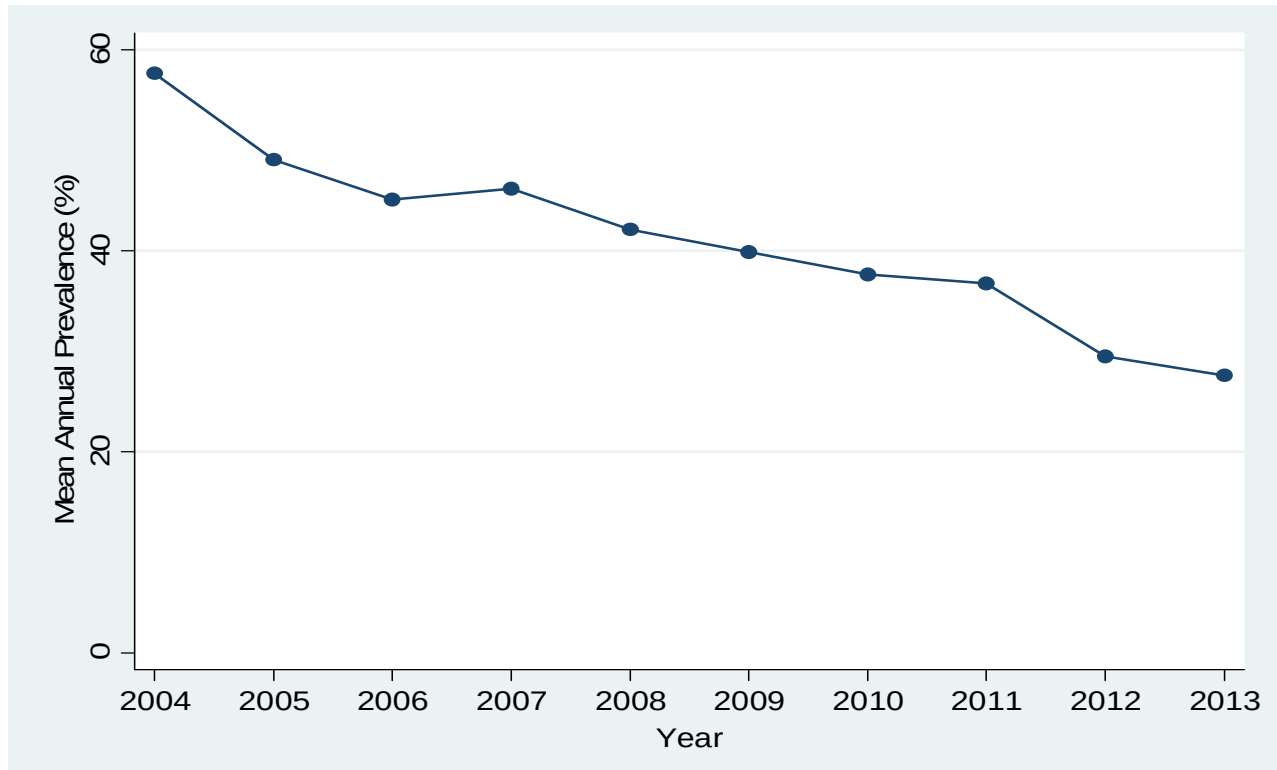


**Figure1: Plot of mean annual prevalence of any OI (of the 17 OIs studied) for the period January 2004 to December 2013.**

The most commonly encountered OIs were geohelminths (35%), diarrhea<1month (18%) and mycobacterium tuberculosis (11%) (Figure2)

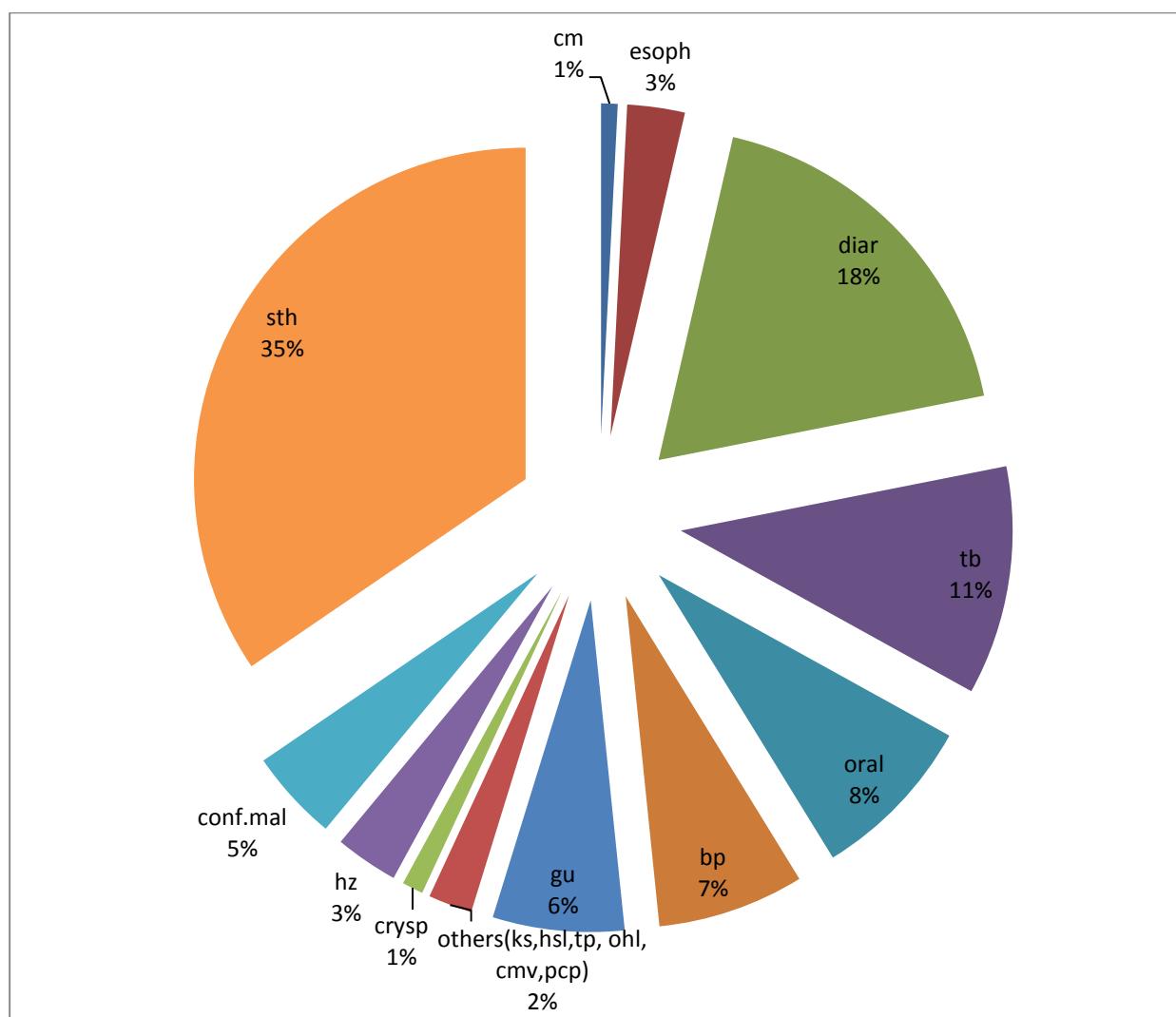


**Figure2: Pie chart showing percent distribution of OI episodes among HIV positive patients on HAART (2004-2013)**

Key: sth=soil transmitted helminth; diar=diarrhea; cm=cryptococcal meningitis; esoph=esophageal candida; tb=tuberculosis; oral=oral candida; bp=bacterial pneumonia; gu=genital ulcer; ks=kaposi sarcoma; hsl=herpes simplex labialis; ohl= Oral hairy leukoplakia; tp=toxoplasmosis; cmv=cytomegalovirus; pcv=pneumocystis carini/jiroveci pneumonia; crysp=cryptosporidiosis; hz=herpes zoster; conf.mal=confirmed malaria

Factors associated with occurrence of any OI are presented in **Table2**. Bivariate and multivariate analyses were performed to identify factors associated with occurrence of any of the 17 OIs among HIV positive patients taking HAART in Uganda. In bivariate analysis, factors independently associated with the occurrence of any OI in the era of HAART were: male gender (cOR<sup>1</sup> 1.13, 95%CI 1.06-1.20); being from Northern Uganda had the greatest risk of suffering an OI (cOR 1.45, 95%CI 1.33-1.47); education above primary was protective (cOR 0.90, 95%CI 0.84-0.98); baseline WHO stages III&IV at HAART initiation was associated with a very high risk of suffering an OI(cOR 4.67, 95%CI 4.33-5.04); patients on Tenofovir (TDF+3TC+NVP/ EFV or TDF+FTC+LPV/r) ART regimes were associated with the lowest risk of suffering an OI (cOR 0.56 95%CI 0.51-0.62); baseline CD4 count

<sup>1</sup> crude odds ratio

>100cells/μl at HAART initiation was protective (cOR 0.57, 95%CI 0.53-0.62); baseline weight at HAART initiation ≥55kg was protective( cOR 0.62, 95% CI 0.57-0.67); patients who enrolled on HAART in the period 2004-2008 had almost 2 times higher risk of suffering an OI compared to patients enrolled on HAART in the period 2009-2013 (cOR 1.8, 95%CI 1.7-1.9).

**Table 2: Bivariate and Multivariate analysis of factors associated with occurrence of any OI among HIV positive patients in the HAART era ( 2004-2013)**

| Variable<br>(n=36,133)            | Any OI<br>present<br>n (%) | cOR(95%CI)       | p-value | aOR(95% CI)      | p-value |
|-----------------------------------|----------------------------|------------------|---------|------------------|---------|
| <b>Sex</b>                        |                            |                  |         |                  |         |
| Female                            | 3,357 (14.1)               | 1                |         | 1                |         |
| Male                              | 1,940 (15.7)               | 1.13 (1.06-1.20) | 0.0001  | 1.21(1.13-1.29)  | <0.0001 |
| <b>Age</b>                        |                            |                  |         |                  |         |
| <35yrs                            | 2,883 (14.9)               | 1                |         | -                | -       |
| ≥35yrs                            | 2,414 (14.4)               | 0.96(0.90-1.02)  | 0.1683  |                  |         |
| <b>Geographical location</b>      |                            |                  |         |                  |         |
| Eastern                           | 1,261 (12.9)               | 1                |         | 1                |         |
| Central                           | 1,361 (14.3)               | 1.13 (1.04-1.23) | 0.0031  | 1.13(1.03- 1.24) | 0.009   |
| Western                           | 1,216 (14.2)               | 1.12(1.03-1.22)  | 0.0099  | 0.96(0.87-1.06)  | 0.426   |
| Northern                          | 1,459 (17.6)               | 1.45(1.33-1.57)  | <0.0001 | 1.78(1.62-1.95)  | <0.0001 |
| <b>Education</b>                  |                            |                  |         |                  |         |
| Primary/none                      | 3,921 (15.0)               | 1                |         | 1                |         |
| ≥secondary                        | 1,098 (13.7)               | 0.91(0.84-0.98)  | 0.0091  | 0.87(0.81-0.94)  | <0.0001 |
| Not recorded                      | 278 (15.5)                 | 1.05(0.92-1.19)  | 0.499   | 0.77(0.67-0.89)  | <0.0001 |
| <b>Marital status</b>             |                            |                  |         |                  |         |
| Single/never married              | 331(15.4)                  | 1                |         | -                | -       |
| Married                           | 2389(13.9)                 | 0.89(0.78-1.00)  | 0.058   |                  |         |
| Divorced                          | 917(15.9)                  | 1.03(0.90-1.19)  | 0.617   |                  |         |
| Widowed                           | 1054(15.2)                 | 0.98(0.86-1.12)  | 0.817   |                  |         |
| Others                            | 322(14.0)                  | 0.90(0.75-1.06)  | 0.198   |                  |         |
| Not recorded                      | 284(15.8)                  | 1.03(0.87-1.23)  | 0.722   |                  |         |
| <b>Occupation</b>                 |                            |                  |         |                  |         |
| Paid employee                     | 809(14.1)                  | 1                |         | -                | -       |
| Self employed                     | 1,768(14.5)                | 1.03(0.95-1.13)  | 0.448   |                  |         |
| Subsistence farmer                | 1,934(14.6)                | 1.04(0.95-1.13)  | 0.424   |                  |         |
| Others                            | 355(15.6)                  | 1.12(0.98- 1.28) | 0.100   |                  |         |
| Not recorded                      | 431(16.1)                  | 1.16(1.03-1.32)  | 0.017   |                  |         |
| <b>Baseline WHO stage</b>         |                            |                  |         |                  |         |
| I&II                              | 926(5.7)                   | 1                |         | 1                |         |
| III&IV                            | 4,371 (22.0)               | 4.67(4.33-5.04)  | <0.0001 | 5.10(4.72-5.50)  | <0.0001 |
| <b>ART regime*</b>                |                            |                  |         |                  |         |
| Stavudine(d4T)                    | 800 (20.4)                 | 1                |         | 1                |         |
| Zidovudine(ZDV)                   | 2,632 (14.5)               | 0.66 (0.61-0.72) | <0.0001 | 0.56(0.44- 0.71) | <0.0001 |
| Tenofovir(TDF)                    | 1,248 (12.6)               | 0.56 (0.51-0.62) | <0.0001 | 0.52(0.39-0.69)  | <0.0001 |
| others                            | 617 (14.9)                 | 0.68 (0.61-0.77) | <0.0001 | 0.55(0.41-0.74)  | <0.0001 |
| <b>Baseline CD4 count</b>         |                            |                  |         |                  |         |
| 0-100                             | 1,051 (20.5)               | 1                |         | 1                |         |
| >100                              | 2,213 (12.9)               | 0.57 (0.53-0.62) | <0.0001 | 0.66(0.61-0.73)  | <0.0001 |
| Not recorded                      | 2,033 (14.7)               | 0.67(0.62-0.73)  | <0.0001 | 0.69(0.63-0.76)  | <0.0001 |
| <b>Weight at start of HAART</b>   |                            |                  |         |                  |         |
| <55kg                             | 2,040 (17.2)               | 1                |         |                  |         |
| ≥55kg                             | 1,370 (11.4)               | 0.62 (0.57-0.67) | <0.0001 | 0.64(0.59-0.69)  | <0.0001 |
| Not recorded                      | 1,887 (15.4)               | 0.87 (0.81-0.93) | 0.0001  | 0.73(0.68-0.79)  | <0.0001 |
| <b>Year of enrolment on HAART</b> |                            |                  |         |                  |         |
| 2004-2008                         | 2,432 (19.6)               | 1.77(1.66- 1.88) | <0.0001 | 3.56(2.83-4.47)  | <0.0001 |
| 2009-2013                         | 2,865 (12.1)               | 1                |         | 1                |         |

\*Stavudine= d4T+3TC+NVP or EFV, Zidovudine=AZT/ZDV+3TC+NVP or EFV, Tenofovir= TDF+3TC+NVPor EFV and TDF+FTC+LPV/r

Variables that were significantly associated with occurrence of any OI among HIV positive patients taking HAART in bivariate analysis were entered into the multivariate logistic regression model and results are as shown in Table 2. Factors significantly associated with occurrence of any OI were: male gender (aOR<sup>2</sup> 1.21, 95%CI 1.13-1.29); being from Northern Uganda still had the greatest risk of suffering an OI (aOR 1.78, 95%CI 1.62-1.95); education above primary was protective (aOR 0.87, 95%CI 0.81-0.94); baseline WHO stages III&IV at HAART initiation was associated with a very high risk of suffering an OI(aOR 5.10, 95%CI 4.72-5.50); patients on Tenofovir (TDF+3TC+NVP/ EFV or TDF+FTC+LPV/r) ART regimes were associated with the lowest risk of suffering an OI (aOR 0.52 95%CI 0.39-0.69); baseline CD4 count >100cells/ $\mu$ l at HAART initiation was protective (aOR 0.66, 95%CI 0.61-0.73); baseline weight at HAART initiation  $\geq$ 55kg was protective( aOR 0.64, 95% CI 0.59-0.69); patients who enrolled on HAART in the period 2004-2008 had almost 2 times higher risk of suffering an OI compared to patients enrolled on HAART in the period 2009-2013 (aOR 3.6, 95%CI 2.8-4.5).

## Discussion

The risk of any OI in an HIV positive patient largely depends on degree of exposure to potential pathogens, the level of host immunity and timely access to antimicrobial prophylaxis[6]. Previous studies show that timely access to HAART (CD4 count>500cell/ $\mu$ l) is highly protective against OIs and associated death[30]. However despite being on HAART, HIV positive patients in resource poor settings may continue to suffer from OIs and related death due to many factors including malnutrition, treatment interruptions, drug interactions, drug adverse effects, poor adherence to ART, drug resistance, delayed access to ART, etc [31]. Our findings are comparable to many other studies in a resource poor settings [32, 33] . Ours is however higher than another study finding by Monosuthi et al who reported an overall prevalence of 8% for all OIs studied after 15 months on HAART[34]. In their study they also found low CD4 count (<50cells/ $\mu$ l), male gender and low body weight strongly associated with occurrence of OIs after HAART[34]. Our findings are also higher than what was found in a related study conducted in Nigeria which reported an overall OI prevalence of 22.4% after 3 years on HAART [35]. The reason for such differences could be due to the difference in the socio demographic characteristics, study period and sample size.

The most common types of OIs among HIV positive patients on HAART in the current study were geohelminths, diarrhea <1 month and tuberculosis. Almost the same were observed in other studies [16-18]. This might be because they are relatively easy to diagnose compare to other OIs. Diarrhoea has for long been reported to be one of the commonest complication in HIV+ individuals associated with opportunistic enteric infections[36]. Previous studies show up to 60% of people living with HIV experience diarrhoea, that negatively affects their quality of life and adherence to HAART[37]. Previous studies elsewhere indicate that diarrhoea may be due to infectious causes (bacterial, viral, protozoal, helminthic, etc) or non-infectious causes(ARV drug effects e.g. ritonavir-boosted protease inhibitors such as Lopinavir/ritonavir or nelfinavir)[37-41]. A previous study in Uganda reported the commonest causes of diarrhoea to be helminthic infections(29.5%), bacterial infections (19.2%) and protozoal infections (9.2%)[42]. Enteric viruses have also been reported associated with diarrhoea[36]. So we

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<sup>2</sup> adjusted odds ratio

suspect in our study diarrhoea<1 month is still a problem partly due to the high prevalence of helminthic infections and partly due to antiretroviral side effects as already shown above. Although morbidity due to helminthic infections can easily be controlled, they are often ignored in adults as most Government interventions target children in schools. We therefore recommend that regular deworming of HIV positive adults should be an integral part of care in HIV/AIDS care programmes in resource poor settings.

Mycobacterium tuberculosis is one of the leading causes of morbidity and mortality in persons infected with HIV/AIDS globally [43]. Studies show that HIV reactivates latent TB hence increasing the risk of TB in HIV-infected patients[44]. In our study we found the frequency of TB to be 11% of the total OI episodes among HIV positive patients on HAART. This might be due to the fact that TB is endemic in sub-saharan Africa and most TB patients in Africa today are also HIV+[43] and by the time they get enrolled on HAART they will have already been registered at TB patients hence the high prevalence observed in our study. A study in Nigeria also found TB and candidiasis were the leading cause of morbidity in the HAART era[35]

Overall, there was a significant declining trend of the mean annual prevalence any OI among HIV positive patients on HAART. However, the study further shows that the burden of OIs was still considerable in spite of availability of HAART. This is probably because these OIs are endemic in the country and will always manifest at the slightest opportunity or they could still occur because of resistance/treatment failure associated with the ART regimen currently in use, poor immunological status at HAART initiation, poor adherence to HAART, poverty and other factors that may comprise the effectiveness of HAART [5, 35, 45-47]. Patients initiating HAART with CD4 -cell counts <50 cells/ $\mu$ l, were found associated with higher risks of OIs while on HAART than patients without such a history [47]. In resource poor settings, HIV patients are more likely to have a higher exposure to infectious agents, have poor nutrition, poor living conditions and health seeking behavior, and poor quality health care than their counterparts in wealthy settings hence poorer ART outcomes [9, 31, 35, 48]. Therefore as suggested by Brooks and colleagues[48], OIs are likely to remain an important aspect of care for persons with HIV/AIDS despite increasing access to HAART as long as the above undermining factors still exists.

Factors independently associated with any OI in the current study were male gender, if from Northern Uganda, low education (<primary), baseline WHO stages III&IV, stavudine ART regimen, baseline CD4 count <100cells/ $\mu$ l, low baseline weight <55kg and period 2004-2008. Similar findings were also observed in other studies elsewhere in Africa [32, 34, 35, 49]. Patients starting ART at advanced HIV disease stage, i.e. with CD4-cell counts <100 cells/ $\mu$ l were more likely to experience an OI, with men being at higher risk for life threatening OIs such as mycobacterium tuberculosis and cryptococcal meningitis compared to women. Therefore in order to improve ART outcomes, there is urgent need to focus on male HIV-positive individuals for early HAART initiation.

## Study limitations

A limitation of this study was the fact that we used secondary data which had been collected not primarily for research purposes. Therefore, some variables which would have been useful for our analysis, like patients' viral loads, monitoring CD4 counts, BMI and ART adherence had substantial missing data entries probably due to high work load of health staff as had been reported previously[50]. This data should be targeted in prospective cohort studies in the future. Another limitation of this study was that only one episode per OI each month was considered per person which may have underestimated the actual risk.

## Conclusion and recommendations

Results from the current study show good progress in the implementation of the HAART programme in Uganda with >90% coverage. However the period overall and OI-specific prevalence varies by time, place and person. The most notable is the prevalence of geohelminths which has not decreased much despite increasing coverage of HAART. We therefore recommend that regular deworming of HIV positive adults should be an integral part of care in HIV/AIDS care programmes in resource poor settings. The main risk factors for the occurrence of any OI after HAART were male gender, if from Northern Uganda, low education (<primary), baseline WHO stages III&IV, stavudine ART regimen, baseline CD4 count <100cells/ $\mu$ l, low baseline weight <55kg and period 2004-2008. Men remain at greater risk of OIs in the era of HAART and should therefore be the main target group for early HAART initiation.

Although, there was a significant declining trend in the mean annual prevalence of any OI with increasing HAART coverage in Uganda, the burden of OIs is still considerable and failure to deal with the effect of poverty and other factors that compromise the effectiveness of HAART means the battle against OIs is still far from being over.

## References

1. Staine JG: **AIDS up date 2007: An overview of acquired immune deficiency syndrome**. New York McGraw-Hill co.,Inc; 2008.
2. UNAIDS: **UNAIDS report on the Global AIDS epidemic 2013**. In. Geneva, Switzerland; 2013.
3. 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**. *American J Trop Med Hyg* 1996, **55**(1):1-11.
4. Holmes B, Losina E, Walensky R, Yazdanpanah Y, Freedberg K: **Review of Human Immunodeficiency Virus Type 1-Related Opportunistic Infections in Sub-Saharan Africa**. *Clinical Infectious Diseases* 2003, **36**:652-662.
5. Mermin J, Were W, Ekwaru J, Moore D, Dawning R, Behumbiize P, Lule JR, Coutinho A, Tappero J, Bunnell R: **Mortality in HIV-infected Ugandan adults receiving antiretroviral treatment and survival of their HIV-uninfected children: a prospective cohort study**. *Lancet* 2008, **371**:752-759.
6. Chaisson R, Moore R: **Prevention of opportunistic infections in the era of improved antiretroviral therapy**. *J Acquir Immune Defic Syndr* 1997, **16**: S14-22.
7. Colebunders R, Latif AS: **Natural history and clinical presentation of HIV-1 infection in adults**. *AIDS* 1991, **5**:S103-112.

8. Selik MR, Starcher ET, Curran JW: **Opportunistic diseases reported in AIDS patients: Frequencies, associations and trends.** *AIDS* 1987, **1**:175-182.
9. 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 Medicine* 2006, **7**:323-330
10. Chaisson R, Gallant J, Keruly J, Moore R: **Impact of opportunistic disease on survival in patients with HIV infection.** *AIDS* 1998, **12**:29-33.
11. CDC: **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Recommendations and Reports 58.** In. CDC, USA; 2009.
12. Watera C, Todd J, Muwonge R, Whitworth J, Nakiyingi-Miiró J, Brink A, Miiró G, Antvelink L, Kamali A, French N *et al*: **Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected adults attending an HIV/AIDS clinic in Uganda.** *J Acquir Immune Defic Syndr* 2006, **42**(3):373-378.
13. Mermin J, Lule J, Ekwaru JP, Malamba S, Downing R, Ransoma R, Kaharuza F, Culver D, Kizito F, Bunnella R *et al*: **Effect of cotrimoxazole prophylaxis on morbidity, mortality, CD4 cell count, and viral load in HIV infection in rural Uganda.** *Lancet* 2004, **364**:1428-1434.
14. Holmes BC, Wood R, Badri M, Margolin S, Wang B, Martens G: **Incidence of primary opportunistic infections in Cape Town South Africa: Implications for prophylaxis.** In: *13th conference of Retroviruses and opportunistic infections: 2005; Denver, USA; 2005.*
15. Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Mourice C, Djomand G, Ackah A, Domoua K, Kadio A *et al*: **Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1 infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial.** *Lancet* 1999, **353**:1469-1475.
16. Walker AS, Ford D, Gilks CF, Munderi P, Ssali F, Reid A, Katabira E, Grosskurth H, Mugenyi P, Hakim J *et al*: **Daily Cotrimoxazole prophylaxis in severely immune-suppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort.** *Lancet* 2010, **375**:1278-1286.
17. UNAIDS: **Guidelines on Cotrimoxazole prophylaxis for HIV-related infections among children, adolescents and adults; Recommendations for a Public health approach** In. Geneva: WHO; 2006.
18. Uganda Ministry of Health: **National AIDS Indicator Survey 2011.** In. Kampala: Uganda Ministry Of Health; 2011.
19. MoFPED UMoF, Planning and Economic Development,: **Millennium Development Goals Report for Uganda 2010.** In. Kampala; 2010.
20. Uganda Ministry of Health: **National policy guidelines for cotrimoxazole prophylaxis for people with HIV/AIDS.** In. Kampala: Ministry of Health; 2005.
21. Uganda Bureau of Statistics: **Uganda Demographic and Health Survey.** In. Calverton Maryland, USA UBOS and Macro International Inc. ; 2006.
22. Kigozi IM, Dobkin LM, Martin JN, Geng EH, Muyindike W, Emenyonu N, ., Bangsberg DR, Hahn JA: **Late-disease stage at presentation to an HIV clinic in the era of free antiretroviral therapy in Sub-Saharan Africa.** *J Acquir Immune Defic Syndr* 2009, **52**(2):280-289.
23. Mills EJ, Bakanda C, Birungi J, Mwesigwa R, Chan K, Ford N, Hogg R, Cooper C: **Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda.** *AIDS* 2011, **25**(6):851-855.
24. Bakanda C, Birungi J, Mwesigwa J, Nachega JB, Chan K, Palmer A, Ford N, Mills EJ: **Survival of HIV-Infected Adolescents on Antiretroviral Therapy in Uganda: Findings from a Nationally Representative Cohort in Uganda.** *PLoS ONE* 2011, **6**(4):e19261.

25. WHO: **Antiretroviral therapy for HIV infection in adults and adolescents; recommendations for a public health approach**. In. Geneva: WHO; 2006.
26. WHO: **Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach 2010 revision**. In. Geneva: WHO; 2010.
27. Uganda Ministry of Health: **Antiretroviral treatment policy**. In. Kampala: Uganda Ministry of Health 2009.
28. **TASO Services and Programmes** [<http://www.tasouganda.org/>]
29. WHO/UNAIDS: **WHO case definition of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children**. In. Geneva: WHO; 2006.
30. WHO: **Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach**. In. Geneva: World Health Organization; 2013.
31. Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, Harries AD: **Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi**. *AIDS* 2006, **20**:2355-2360.
32. Moges N, Kassa M: **Prevalence of Opportunistic Infections and Associated Factors among HIV Positive Patients taking Anti-Retroviral Therapy in DebreMarkos Referral Hospital, Northwest Ethiopia**. *J AIDS Clin Res* 2014, **5**:301.
33. Sun HY, Chen MY, Hsieh SM, Sheng WH, Chang SY, Hsiao CF, Hung CC, Chang SC: **Changes in the clinical spectrum of opportunistic illnesses in persons with HIV infection in the era of highly active antiretroviral therapy**. *Jpn J Infect Dis* 2006, **59**:311-316.
34. Manosuthi W, Chaovavanich A, Tansphaswadikul S, Prasithsirikul W, Inthong Y, Chottanapund S, Sittibusaya C, Moolasart V, Termvises P, Sungkanuparph S: **Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV infected patients in a resource-limited setting**. *Journal of Infection* 2007, **55**:464-469.
35. Iroezindu M, Ofondu E, Hausler H, VanWyk B: **Factors for Opportunistic Infections in HIV Patients Receiving Antiretroviral Therapy in a Resource-Limited Setting in Nigeria**. *J AIDS Clin Res* 2013, **S3**:002.
36. Grohmannp G, Glass R, Pereira H, Monroem s, Ainerweber AH, Bryan A: **Enteric Viruses And Diarrhea In Hiv-Infected Patients**. *The New England Journal of Medicine* 1993, **329**(1):14-20.
37. MacArthur R, DuPont H: **Etiology and Pharmacologic Management of Noninfectious Diarrhea in HIV-Infected Individuals in the Highly Active Antiretroviral Therapy Era**. *Clinical Infectious Diseases* 2012, **55**(6):860-867.
38. Guest J, Ruffin C, Tschampa J, DeSilva K, Rimland D: **Differences in Rates of Diarrhea in Patients with Human Immunodeficiency Virus Receiving Lopinavir-Ritonavir or Nelfinavir**. *Pharmacotherapy* 2004, **24**(6):727-735.
39. Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, Lichtenstein K, Wirtz V, Rightmire A, Odesloo L *et al*: **96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures**. *AIDS* 2006, **20**(5):711-718.
40. Heiser C, Ernst J, Barrett J, French N, Schutz M, Dube M: **Probiotics, soluble fiber and L-glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)- related diarrhea**. *J Int Assoc Physicians AIDS Care* 2004, **3**: 121 – 129.
41. Molina J, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, Moyle G, Mancini M, Percival L, Yang R *et al*: **Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of**

- antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008, **372**(9639):646–655.
42. Binka A, Mahe C, Watera C, Lugada E, Gilks CF, Whitworth JAG, French N: **Diarrhoea, CD4 Counts and Enteric Infections in a Community-Based Cohort of HIV-Infected Adults in Uganda.** *Journal of Infection* 2002, **45**(2):99-105.
  43. WHO: **Global Tuberculosis Control Report 2013.** In. Geneva, Switzerland: WHO; 2013.
  44. Selwyn A, Hartel D, Lewis VA, Schoenbaum E, Vermund S, Klein R, Walker A, Friedland G: **A Prospective Study of the Risk of Tuberculosis among Intravenous Drug Users with Human Immunodeficiency Virus Infection.** *New England Journal of Medicine* 1989, **320**(9):545-550.
  45. Bonnet F, Lewden C, May T, Heripret C, Jouglu E, Bevilacqua S, Costagliola D, Salmon D, Chene G, Morlat P: **Opportunistic infections as cause of death in HIV infected patients in the HAART era in France.** *Scand J Infect Dis* 2005, **37**:482-487.
  46. Manzardo C, Zaccarelli M, Agüero F, Antinori A, Mirro JM: **Optimal timing and best antiretroviral regimen in treatment-naïve HIV-infected individuals with advanced disease.** *Journal of Acquired Immune Deficiency Syndrome* 2007 **46**:S9–S18.
  47. Fielden SJ, Rusch ML, Levy AR, et al.: **Predicting hospitalization among HIV-infected antiretroviral naïve patients starting HAART: Determining clinical markers and exploring social pathways.** *AIDS Care* 2008, **20**:297–303.
  48. Brooks J, Kaplan J, Holmes K, Benson C, Pau A, Masur H: **HIV-associated opportunistic infections--going, going, but not gone: the continued need for prevention and treatment guidelines.** *Clin Infect Dis* 2009, **48**(5):609-611.
  49. Ledergerber B, Egger M, Etard V, Weber R, Hirschel B, Furrer H, Battegay M, Vernazza P, Bernasconi E, Opravil M *et al*: **AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV cohort study.** *J Amer Med Assoc* 1999, **282**:2220-2226.
  50. Kiragga NA, Castelnovo B, Schaefer P, Muwonge T, Easterbrook JP: **Quality of data collection in a large HIVobservational clinic database in sub-Saharan Africa: implications for clinical research and audit of care.** *Journal of the International AIDS Society* 2011, **14**:3.