Nuwagira et al., HIV Curr Res 2018, 3:2
DOI: 10.4172/2572-0805.1000129

HIV: Current Research

Research Article Open Access

Predictors of Loss to Follow up among HIV Infected Patients Initiated on Second Line ART in Southwestern Uganda

Nuwagira E*, Rhoda Winnie M, Amir A and Muzoora C

Mbarara University of Science and Technology, Mbarara, Uganda

Abstract

Background: There is an increasing need for second-line therapy in resource-limited settings in sub-Saharan African countries. We sought to describe the one-year incidence of loss to follow up and mortality among patients taking second line ART at an experienced ART program in southwestern Uganda.

Methods: A retrospective cohort study was conducted at Mbarara Regional Referral Hospital mHIV clinic among adults who started second line ART between 2002 and 2017. We assessed social-demographic, clinical and laboratory variables routinely collected at the initiation of msecond line ART. Variables that had a $p<0.05$ in unadjusted bivariate analyses were included into a multivariate binomial regression model using a step wise backward selection procedure to describe the factors that independently predicted loss to follow up and mortality at $p<0.05$

Results: Records from 921 patients (56.1% females) were analysed; their mean age ± SD was 37.6 ± 9 years. More than half (52.5%) had a CD4 T cell count less than 100 cells/µl at the start of second line. The incidence of loss to follow up was 26.7 per 100 person years. Male sex (Adjusted risk ratio (ARR)=1.7, 95% CI 1.2-2.4) p=0.003, medical history of Cryptococcus meningitis (ARR=3.5, 95% CI 1.7-7.0) p<0.001 and Haemoglobin less than 10 g/dl (RR=1.3 95% C.I: 1.1-2.7 p=0.008 were strongly associated with loss to follow up.

Conclusions: There is a high incidence of loss to follow up among patients taking second line ART at a tertiary ART center in South-Western Uganda.

Keywords: HIV; Loss to follow up; Second-line; Antiretroviral therapy

Introduction

Approximately 21.8 million people living with HIV (PLWH) were on antiretroviral therapy (ART) worldwide by the end of June 2017 [1]. The increasing volume of treatment failure among patients on first line ART and expanding HIV viral load monitoring [2] has resulted into an escalating need for second line therapy which is expected to rise to three times the current state by 2030 [3]. Second line ART agents are costly and not readily available to most ART care givers. Failure on second line ART will increase the risk of mortality [4] or progression to the current last resort which is third line therapy that is even much more expensive than second line [5] and is not readily available in our setting [6]. Studies have shown that LTFU is indeed a major challenge for ART programs in resource limited settings [7] because of its association with treatment disruption, subsequent ART failure and mortality [8]. Failure on potent regimens like second line ART coupled with an increased demand for subsequent regimens that are costly or not available hampers chances of achieving the last 90' and HIV eradication by 2030. Currently there is no peer reviewed data about the loss to follow up among HIV infected patients on second line ART in Uganda. With the increasing need to preserve the WHO recommended second line ART for those failing on first line ART, there is need to study the trends of loss to follow up among those taking second line ART and retain them in care for as long as possible. We sought to determine the one-year incidence rate of loss to follow up, and to explore the socio-demographic factors and clinical characteristics associated with loss to follow up among patients taking second line ART in Uganda. Knowledge from this study would help us design targeted interventions to increase retention and prolong care and reduce the need for third line ART among the patients on second line ART at a risk of being LTFU.

Methods

Study site

The study was conducted at Mbarara Regional Referral Hospital (MRRH) which is located in Mbarara Municipality, about 260 kilometres from Kampala, the capital city of Uganda. MRRH serves as the teaching hospital for Mbarara University of Science and Technology and has the biggest HIV clinic in south western Uganda which provides both paediatric and adult HIV services to approximately thirty thousand patients. Patients' information is digitized into an electronic Medical Records system (open MRS). This information includes a section of social demographic characteristics, clinical examination findings, laboratory values, records of treatment refill and adherence, all filled/updated by clinicians at every patient's clinical visit. In this clinic, patients are counselled at the time first line ART is initiated, followed up and further adherence counselling done at the time they are switched to second line. Patients are usually given drug refills of up to three months and adherence is monitored by using self-reported and electronic adherence calculation, using the pill count method.

Study population

We retrospectively collected data and included adolescents (>15

***Corresponding author:** Edwin Nuwagira, MBChB, MMed, Mbarara University of Science and Technology, Mbarara, Western Uganda, Tel: +256779096887; E-mail: edwinuwagira@gmail.com

Received September 17, 2018; **Accepted** October 12, 2018; **Published** October 25, 2018

Citation: Nuwagira E, Winnie MR, Amir A, Muzoora C (2018) Predictors of Loss to Follow up among HIV Infected Patients Initiated on Second Line ART in Southwestern Uganda. HIV Curr Res 3: 129. doi: 10.4172/2572-0805.1000129

years) and adults living with HIV who had evidence of failure on first line ART and had been initiated on second-line ART containing a protease inhibitor between 2002 and 2017. Only patients who had been enrolled in care on second line ART for at least one year were included in the study. Patients who were taking second line ART but had never taken first line ART were excluded. No data beyond one year of enrolment was reviewed.

Data extraction

We formulated a data collection tool (Appendix 1) that included all the baseline variables we were interested in to answer our objectives. These were the same characteristics recorded on the case sheets/paper file during clinic visits at the beginning of second line ART. Since our data base is an open MRS database, we integrated SQL queries in STATA version 13 to run over the data base and collect/compile patients who were on second line ART and above 15 years. These were then transferred to a separate STATA do file. We again used the SQL queries to generate the variables we needed and generated a cleaner do file with only patients above 15 years, on second line ART with the variables of interest.

Quality assurance

The HIV clinic data team has its own quality assurance to ensure collection of accurate data. The data managers generated a Quality Control (QC) code in the open MRS that identifies any inconsistency in data. Queries related to data entry are worked on by the data team during their weekly meetings. In addition to the internal quality control we pulled every 20th number of the extracted data and cross-checked with the corresponding paper file to compare the information. Also whenever information extracted from the database was not clear, we still double checked with the files and we consulted the relevant clinicians in case both the files and database were not clear.

Ethical consideration

This work was done after acquiring all the necessary ethical approval from the Faculty of Medicine at Mbarara University of Science and Technology (MUST), MUST research committee and the MRRH Director (Appendix 2). All data used was de-identified using the MRRH HIV clinic identification number, and our study generated identification number.

Data analysis

Since the data was generated into STATA version 13 during extraction, we used the same software for analysis.

Categorical variables were expressed as proportions whereas continuous variables were expressed as means with a standard deviation if normally distributed and, median with an interquartile range for skewed data to describe socio-demographic, clinical and laboratory characteristics at the start of second line ART.

To find the incidence of loss to follow up, we calculated every participant's person time in months. We then counted the number of events (loss to follow up) per person time. The time was then converted to person years and parameters were given a 95% confidence interval for reliability of our results. We also calculated the incidence proportions in percentage where the numerator included patients who were dead or lost to follow within 12 months from the day of starting second line ART, whereas the denominator included all those who had been switched to a second line ART regimen and completed at least one year on second line ART (Including those lost to follow up, dead, transferred out and those active in care).

We used the baseline demographics, clinical examination findings and laboratory values like CD4, haemoglobin and Total lymphocyte count to independently generate factors associated with LTFU using a binomial regression model giving us risk ratios. Our outcome of interest (loss to follow up), was expressed as binary variables. We set up the analysis so that for each variable, the reference category was that which we hypothesized to have the lowest risk of LTFU. For example; having Stage one HIV was thought to be associated with retention into care, thus used as the reference range for that category. Sex and other factors that had a p-value less than 0.05 in the bivariate analysis were included in the multivariate analysis using a binomial regression model that was performed in a backward stepwise selection method to determine significant independent predictors of LTFU. Adjusted risk ratios with associated 95% confidence intervals were calculated. Factors that had a p value of 0.05 or less were considered to be significant. The sex variable was included into the multivariate model even when it did not have a p value less than 0.05 in bivariate analysis as a priori.

Results

We reviewed records of 29,000 HIV positive patients. Of the 1121 participants who had been initiated on second line ART since 2002 to 2017, a total of 200 patients were excluded (150 had not completed one year, 42 had no known 2nd line start date and 8 had not had any baseline information recoded). We analysed records from 921 participants who met the study inclusion criteria (Figure 1).

Baseline characteristics

Of the 921 participants, 517 (56.1%) were females with a mean ± SD age of 37.6 ± 9.2 years. majority of the participants were between 35 and 49 years of age and at the start of second line ART the median CD4 count at switch was 95 cells/mm^3 (IQR 47-195) for all participants (Table 1).

Loss to follow up

The rate of LTFU one year after switching to 2nd line ART regimen

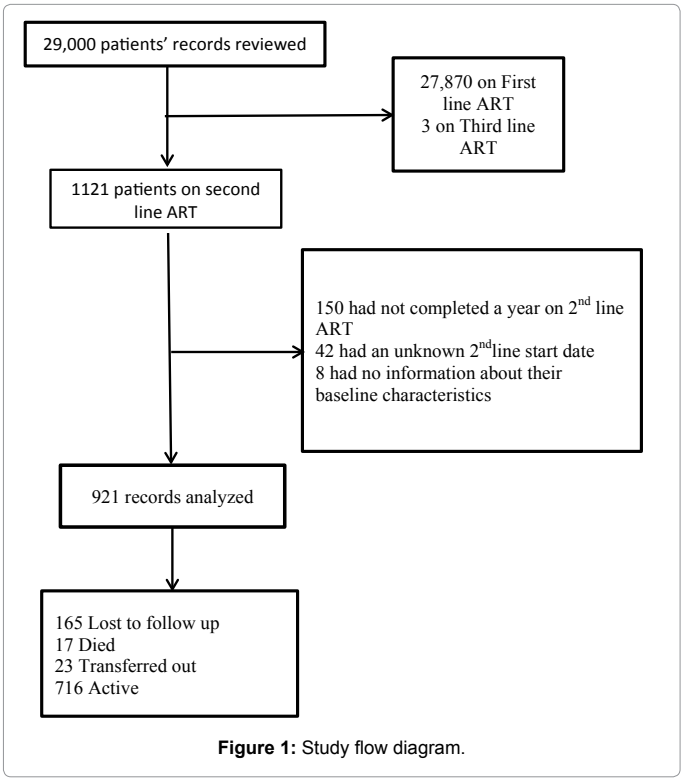

Figure 1: Study flow diagram.

Characteristic	N**	
Age in years, mean (SD)	921	37.6 ± (9.2)
Female gender n (%)	921	517 (56.1)
Baseline CD4 cells/mm³ median (IQR)	834	95 (47-195)
BMI in kg/m² mean (SD)	684	21.6 (4)
Viral load (copies/ml) median (IQR)	445	35400 (11200-118270)
Baseline lymphocyte count median (IQR)	782	1.0 (0.45-1.78)
Baseline Hemoglobin (g/dl), mean ± (SD)	782	12.8 ± 2.1
Switch criteria n (%)	826	
Clinical failure		259 (31.4)
Immunological failure		322 (37.7)
Virological failure		266 (32.2)
Marital status n (%)	863	
Single		425 (49.1)
Married		438 (50.7)
Living children/ Dependents Median (IQR).	703	3 (1-4)
Education Status n (%)	474	
None		25 (5.3)
Primary		232 (48.9)
Secondary		152 (32.0)
Tertiary		65 (13.7)
Employed n (%)	848	753 (81.8)
Time to clinic	446	
<30 min		91 (20.4)
30-60 min		146 (32.7)
1-2 hours		137 (30.7)
2-3 hours		56 (12.6)
>3 hours		16 (3.6)
Poor Adherence status, n (%)	921	
Alcohol Intake, n (%)	482	
Yes		119 (24.7)
No		363 (75.3)
First Line ART Backbone, n (%)	921	
D4T or DDI based		357 (38.8)
AZT and3TC based		418 (45.4)
3TC and TDF		146 (15.8)
History of Opportunistic Infections	114	
Kaposi's Sarcoma		32 (28.1)
Cryptococcal meningitis		10 (8.7)
Tuberculosis		72 (63.2)
**N varies per variable with the maximum being 921 due the number of observations after excluding those with missing data.		

Table 1: Socio-demographic, clinical and laboratory characteristics at the start of second line ART.

was 26.7 per 100 person years after a total follow up time was 617 years. One hundred and sixty-five (165) 17.9% of the 921 participants enrolled in our study were lost to follow up.

Factors associated with loss to follow up

In bivariate analysis, the following characteristics had a p value of 0.05 or less; male gender, age category of 24-43, and 35-49, patient categories (Transferred in versus the continuing cohort of patients), a haemoglobin less than or equal to 10 g/dl, and viral load above 500. They were included in a multivariate binomial regression model as described in section 3.9. Males had a 1.7-fold risk for dropping out of care when compared to females (95% C.I: 1.2-2.4 p=0.002). Other factors that were independently associated with loss to follow up include: haemoglobin level less than 10 g/l (aRR 1.8 95% C.I: 1.1-2.7 p=0.006) and a history of Cryptococcal meningitis (aRR 3.2 95% C.I: 1.3-3.4 p<0.001) were independently associated with loss to follow up (Table 2).

Discussion

In our study, the incidence of loss to follow up was 26.7 per 100 person years (17.9%). These are high figures compared to a South African cohort study where the loss to follow up in one year among patients on second line ART was 10.2% [9]. Another study conducted in Ethiopia found that the loss to follow up was between 11.6 per 100 person years [10] and 18.9% after 22.2 months of follow up [11]. The factors that were independently associated with loss to follow up in our study were being a male, a history of Cryptococcal meningitis, low baseline hemoglobin count, history of taking either Stavudine or Didanosine, and switching to second line ART due to clinical criteria. This is not different form other studies done in sub Saharan Africa which have shown that young males [12] with advanced WHO clinical stage [10,13], are most likely to be lost to follow up. This young population starting on second line therapy is most likely to face adherence challenges, also known as "treatment fatigue" [12,14] hence the high risk of loss to follow up. Our study found that patients who had taken Stavudine or Didanosine as part of the first line regimen had a 2-fold risk of being lost to follow up compared to the current standard back bone of first line ART (3TC/TDF). This is a reflection of the effect of total duration of ART since Stavudine and Didanosine

Characteristic	Active n (%)	LTFU n (%)	Unadjusted risk ratio [C I]	P values	Adjusted Risk Ratios [C.I] N=745	p values
Male gender	309 (79.6)	80 (20.5)	1.1 [0.9-1.5]	0.21	1.7 [1.2-2.4]	0.003
Age Category n (%)						
18-24	47 (65.3)	25 (34.7)	1			
25-34	211 (81.8)	47 (18.2)	0.5 [0.3-0.8]	0.002		
35-49	385 (83.3)	77 (16.7)	0.5 [0.3-0.7]	0.001		
≥50	73 (82)	16 (18)	0.5 [0.3-0.9]	0.02		
Patient Category						
Original cohort	557 (85)	99 (15)	1			
Transfer in	159 (70.7)	66 (29.3)	1.9 [1.4-2.5]	0		
CD4 categories						
<100	348 (84.1)	66 (15.9)	1			
100-250	207 (84.2)	39 (15.8)	1 [0.7-1.4]	0.97		
251-500	83 (83.8)	16 (16.2)	1 [0.6-1.6]	0.96		
>500	35 (94.6)	2 (5.4)	0.3 [0.1-1.3]	0.12		
BMI in kg/m²						
Underweight	106 (77.4)	31 (22.6)	1			
Normal BMI	349 (87.3)	51 (12.7)	0.5 [0.4-0.8]	0.05		
Overweight	74 (89.2)	9 (10.8)	0.5 [0.2-0.9]	0.06		
Obese	25 (86.4)	4 (13.8)	0.6 [0.2-1.6]	0.31		
Viral load category						
<500	30 (81.1)	7 (18.9)	1			
>500	359 (91)	36 (9)	0.5 [0.2-1]	0.05		
Switch criteria n (%)						
Virological failure	238 (92.3)	20 (7.7)	0.4 [0.2-0.9]	0.02	0.6 [0.24-.4]	0.298
Clinical failure	174 (69.6)	76 (30.4)	1.9 [1.1-3.2]	0.01	2.9 [1.4-6]	0.004
Immunological failure	268 (85)	32 (10.7)	1			
Marital status						
Single	323 (79.9)	81 (2.17)	1.1 [0.8-1.5]	0.43		
Married	344 (82.1)	75 (17.9)	1			
Missing	49 (84.4)	9 (15.6)	0.8 [0.5-1.6]	0.65		
Hemoglobin						
>10 g/dl	579 (86)	94 (13.7)	1			
<10 g/dl	55 (76.4)	17 (23.6)	1.8 [1-2.6]	0.02	1.8 [1.1-2.9]	0.008
Alcohol History						
Yes	88 (80.7)	21 (19.3)	1.0 [0.6-1.5]	0.98		
No	278 (80.8)	66 (19.2)	1			
Missing	350 (81.8)	78 (18.2)	0.9 [0.7-1.2]	0.73		
First Line ART Backbone						
D4T or DDI	273 (78.7)	74 (21.3)	1.6 [1.0-2.6]	0.04	2.4 [1.2-4.6]	0.01
AZT and 3TC	328 (81.6)	74 (18.4)	1.4 [0.9-2.3]	0.15	1.9 [1.0-3.8]	0.05
3TC and TDF	115 (87.1)	17 (12.9)	1			
Occupation						
Unemployed	67 (76.1)	21 (23.9)	1			
Employed	449 (82.2)	97 (17.8)	0.7 [0.5-1.1]	0.16		
Missing	52 (75.4)	17 (24.6)	1.0 [0.6-1.8]	0.9		
Partner status						
Negative	29 (76.3)	9 (23.7)	1.2 [0.6-2.1]	0.54		
Positive	155 (82.4)	33 (17.6)	0.9 [0.6-1.2]	0.53		
Unknown	425 (80.3)	104 (19.7)	1			
Missing	107 (84.9)	19 (15.1)	0.7 [0.4-1.2]	0.25		
History of K.S	24 (77.4)	7 (22.6)	1.2 [0.6-2.3]	0.57		
History of TB	53 (80.3)	13 (19.7)	1.1 [0.6-1.7]	0.83		

Table 2: Factors associated with loss to follow up among patients initiated on second line ART at MRRH HIV Clinic.

were later discontinued, as part of the backbone of first line ART by WHO in 2009 [15]. This has also been documented in peer reviewed literature that patients enrolled on ART before 2008, were more likely to be lost to follow up compared to those enrolled after 2008 [16,17]. Unlike previous literature showing that a low CD4 [11,12,18] and low T lymphocyte count [16] predict loss to follow up in first line ART, we did not find the two laboratory tests associated with LTFU, however a low baseline Hemoglobin count was associated with loss to follow up and this confirms the findings by Asiimwe et al. also done at MRRH [16]. Our study, however, used the WHO recommended cut off of less than or equal to 10 g/dl [19], compared to the 11 g/dl used by Asiimwe et al. We also found out that there was a longer duration on first line ART prior to switching to second line ART compared to other studies in South Africa like the Shearer et al. study (43 months versus 18.8 months) [9]. Studies have shown that the mortality among patients who delay switching to second line is high, up to 11.9% [20]. This is

attributed to the limited access to viral load testing in low resource centres (Richard Murphy et al. 2017). Patients that receive second line ART late are sicker and more likely to be lost to follow up. These studies, however, had different definitions of loss to follow up and it has been noted that results of retention proportions presented are often affected by the choice of LTFU definition [21], for example Pujandes et al. considered LTFU when the time between the last visit and the closing date of the corresponding cohort was greater than one year [22]. Our study used a universally acceptable definition of LTFU in HIV care programs by Chi et al. so that our results can be generalizable to other HIV treatment centers that provide second line ART. We were limited by missing information about the true outcomes of the patients who had been lost to follow up, hence making it hard for us to differentiate between lost to follow up and mortality [23].

Conclusion and Recommendations

Our findings show that there is a high incidence of loss to follow up this is due to late detection of treatment failure thus long duration on first line ART. We recommend designing and validating a clinical prediction tool using the above identified factors for easy identification of patients on second line ART who would need active follow up, to improve retention of patients on second line ART in our HIV treatment program. We recommend active follow up of these patients initially lost to follow up to ascertain their true outcomes. Finally, we recommend further studies that evaluate the relationship between moderate to severe anaemia among patients on second line ART loss to follow up.

Conflict of Interest

The Authors have no conflict of interest to declare.

References

1. UNAIDS, Joint United Nations Programme on HIV/AIDS (UNAIDS), Fact Sheet 2016. Geneva, Switzerland: UNAIDS.
2. Haas AD, Keiser O, Balestre E, Brown S, Bissagnene E, et al. (2015) Monitoring and switching of first-line antiretroviral therapy in adult treatment cohorts in sub-Saharan Africa: collaborative analysis. The Lancet HIV 2: e271-e278.
3. Estill J, Ford N, Salazar-Vizcaya L, Haas AD, Blaser N, et al. (2016) The need for second-line antiretroviral therapy in adults in sub-Saharan Africa up to 2030: a mathematical modelling study. The Lancet HIV 3: e132-e139.
4. Ajose O, Mookerjee S, Mills EJ, Boulle A, Ford N (2012) Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. AIDS 26: 929-938.
5. Meyer-Rath G, Pillay Y, Mark B, Alana B, Lawrence L, et al. (2010) Total cost and potential cost savings of the national antiretroviral treatment (ART) programme in South Africa 2010 to 2017. XVIII international AIDS conference.
6. IRIN (2011) Striving to provide first-, second- and third-line ARVs. The inside story on emergencies.
7. Rachlis B, Ochieng D, Geng E, Rotich E, Ochieng V, et al. (2015) Evaluating outcomes of patients lost to follow-up in a large comprehensive care treatment program in western Kenya. J Acquir Immune Defic Syndr 68: e46-e55.
8. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, et al. (2018) Outcomes of Patients Lost to Follow-up in African Antiretroviral Therapy Programs: Individual Patient Data Meta-analysis. Clinical Infectious Diseases.
9. Shearer K, Evans D, Moyo F, Rohr JK, Berhanu R, et al. (2017) Treatment outcomes of over 1000 patients on second-line, protease inhibitor-based antiretroviral therapy from four public-sector HIV treatment facilities across Johannesburg, South Africa. Trop Med Int Health 22: 221-231.
10. Assemie, MA, Muchie KF, Ayele TA (2018) Incidence and predictors of loss to follow up among HIV-infected adults at Pawi General Hospital, northwest Ethiopia: Competing risk regression model. BMC Research Notes 11: 287.
11. Wilhelmson S, Reepalu A, Tolera Balcha T, Godana Jarso G, Bjorkman P (2016) Retention in care among HIV-positive patients initiating second-line antiretroviral therapy: A retrospective study from an Ethiopian public hospital clinic. Glob Health Action 9: 29943.
12. Arnesen, R, Moll AP, Shenoi SV (2017) Predictors of loss to follow-up among patients on ART at a rural hospital in KwaZulu-Natal, South Africa. PLoS One 12: e0177168.
13. Tsegaye E, Worku A (2011) Assessment of antiretroviral treatment outcome in public hospitals, South Nations Nationalities and Peoples Region, Ethiopia. Ethiopian Journal of Health Development 25:102-109.
14. Claborn KR, Meier E, Miller MB, Leffingwell TR, et al. (2015) A systematic review of treatment fatigue among HIV-infected patients prescribed antiretroviral therapy. Psychol Health Med 20: 255-265.
15. World Health Organization (2010) Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach-2010 revision. 2010.
16. Asiimwe SB, Kanyesigye M, Bosco Bwana M, Okello S, Muyindike W (2015) Predictors of dropout from care among HIV-infected patients initiating antiretroviral therapy at a public sector HIV treatment clinic in sub-Saharan Africa. BMC Infect Dis 16: 43.
17. Eguzo, KN, Lawal AK, Umezurike CC, Eseigbe CE (2015) Predictors of Loss to Follow-up among HIV-infected Patients in a Rural South-Eastern Nigeria Hospital: A 5-year Retrospective Cohort Study. Ann Med Health Sci Res 5: 373-378.
18. Meloni ST, Chang C, Chaplin B, Rawizza H, Jolayemiet O, et al. (2014) Time-dependent predictors of loss to follow-up in a large HIV treatment cohort in Nigeria. Open Forum Infect Dis 1.
19. Khusun H, Yip R, Schultink W, Dillon DH (1999) World Health Organization hemoglobin cut-off points for the detection of anemia are valid for an Indonesian population. The Journal of Nutrition 129: 1669-1674.
20. Ssempijja V, Nakigozi G, Chang L, Gray R, Wawer M, et al. (2017) Rates of switching to second-line antiretroviral therapy and impact of delayed switching on immunologic, virologic, and mortality outcomes among HIV-infected adults with virologic failure in Rakai, Uganda. BMC Infect Dis 17: 582.
21. Shepherd BE, Blevins M, Vaz LM, Moon TD, Kipp AM, et al. (2013) Impact of definitions of loss to follow-up on estimates of retention, disease progression, and mortality: Application to an HIV program in Mozambique. Am J Epidemiol 178: 819-828.
22. Pujades-Rodríguez M, Balkan S, Arnould L, Brinkhof MA, Calmy A, et al. (2010) Treatment failure and mortality factors in patients receiving second-line HIV therapy in resource-limited countries. JAMA 304: 303-312.
23. Chi BH, Yiannoutsos CT, Westfall AO, Newman JE, Zhou J, et al. (2011) Universal definition of loss to follow-up in HIV treatment programs: A statistical analysis of 111 facilities in Africa, Asia, and Latin America. PLoS Med 8: e1001111.