Demographic characteristics and opportunistic diseases associated with attrition during preparation for antiretroviral therapy in primary health centres in Kibera, Kenya

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Summary Using routine data from HIV-positive adult patients eligible for antiretroviral therapy (ART), we report on routinely collected demographic characteristics and opportunistic diseases associated with pre-ART attrition (deaths and loss to follow-up). Among 2471 ART eligible patients, enrolled between January 2005 and November 2008, 446(18%) were lost to attrition pre-ART. Adjusted risk factors significantly associated with pre-ART attrition included age <35 years (Odds Ratio, OR 1.4, 95% Confidence Interval, CI 1.1–1.8), severe malnutrition (OR 1.5, 95% CI 1.1–2.0), active pulmonary tuberculosis (OR 1.6, 95% CI 1.1–2.4), severe bacterial infections including severe bacterial pneumonia (OR 1.9, 95% CI 1.2–2.8) and prolonged unexplained fever (>1 month), (OR 2.6, 95% CI 1.3–5.2). This study highlights a number of clinical markers associated with pre-ART attrition that could serve as 'pointers' or screening tools to identify patients who merit fast-tracking onto ART and/or closer clinical attention and follow-up.

keywords risk factors, attrition, pre-ART phase

Introduction

Many operational challenges still hinder the goal of achieving timely universal access to antiretroviral therapy (ART) in sub-Saharan Africa. One such challenge is high attrition (deaths and loss to follow-up) among patients during the pre-ART phase, both those not yet ART eligible and those eligible and in the preparation phase for ART (Lawn *et al.* 2005, 2008; Ingle *et al.* 2010a; Larson *et al.* 2010; Zachariah *et al.* 2010). Finding ways forward to reduce attrition in these two groups is essential as attrition here is a proxy indicator of health system and programme barriers to accessing care. Pre-ART attrition, particularly among those considered eligible for ART, is particularly important as this is a highly vulnerable group that is at high risk of death. These are thus patients who have contact with the health system but for various reasons do not manage to pass through the ART 'gates' to access life-saving treatment.

There is a dearth of published information on the association between opportunistic diseases and pre-ART attrition among ART eligible patients. Such information would be useful for identifying specific patient groups who should receive priority attention and targeted interventions to improve their retention in care and expedite ART access. Using routine data from the Médecins Sans Frontières (MSF) supported HIV/AIDS programme in Kibera, Kenya, we report on demographic characteristics and opportunistic diseases associated with attrition among ART eligible adults before starting ART.

Methods

Study design

This was a retrospective cross-sectional study of routinely collected programme data.

Study setting and population

The study was conducted in Kibera, an urban slum setting in Kenya with an estimated population of about 200 000 inhabitants. Migration is common in this slum, and a considerable proportion of the working population consists

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of daily migrant workers. Thus, this population is generally mobile because of the contextual situation.

In Kibera, MSF works in close collaboration with the Ministry of Health, providing HIV/AIDS care and treatment in three comprehensive primary care clinics. This analysis included all HIV-positive adult patients (≥15 years) who were ART eligible at the time of presenting to these clinics between January 2005 and November 2008.

Referral to the HIV clinic, clinical assessment and ART eligibility

Patients attend the HIV/AIDS and ART clinic either at their own will after having been diagnosed elsewhere or because they are formally referred by other health facilities. There are also stand-alone HIV testing sites where patients undergo HIV testing and are subsequently encouraged to present to the HIV/AIDS clinic for clinical assessment.

At presentation to the clinics, all patients underwent a complete assessment during which height and weight were measured and a full clinical history and examination conducted to determine WHO HIV diseases staging and the presence of opportunistic diseases (all clinicians have been trained in the diagnosis and management of opportunistic diseases with regular supervision). HIV-positive adult patients were considered eligible for ART if they were in WHO clinical stage 3 (either with a CD4 count <350 cells/mm^3 or with unknown CD4 count) or stage 4 (irrespective of CD4 count), or with a CD4 count <200 cells/mm^3 (irrespective of WHO staging) (NASCOP 2005). ART eligible patients received preliminary counselling, returned home and then returned to prepare for ART initiation, accompanied by a guardian, if possible, to foster a supportive home environment and reinforce the importance of treatment adherence. Patients attended individual counselling sessions to be educated on HIV infection and the implications of ART. For HIV-TB co-infected patients, care and treatment for TB is provided in the same health facility by the same clinician.

There were no active tracing systems in place to trace patients in the pre-ART phase. The tracing system (like many others in Africa) only focused on tracing patients once they had been placed on ART. Thus, existing mechanisms for tracing only get activated once a patient has managed to receive ART and not before.

Data collection, patient outcomes and statistical analysis

Information on demographic characteristics and clinical data (height, weight, WHO stage, and opportunistic diseases) on initial assessment were obtained from an HIV/AIDS software program (FUCHIA, Epicentre, Paris, France) into which data is entered daily using standardised data collection sheets in the clinics. Treatment outcomes were defined and analysed as follows: Attrition pre-ART included all patients who died or were lost to follow-up; death was defined as a patient who died for any reason during the preparatory phase; lost to follow-up was defined as a patient who never returned to the ART facility for a period of 1 month or more after the last scheduled appointment date. There were no active tracing systems in place to trace patients in the pre-ART phase. Patients were regarded as being alive and under follow-up if (i) they were alive and on ART, and thus by definition had passed through the pre-ART phase, or (ii) were still alive and waiting to start ART. Outcomes for ART eligible patients still waiting to start ART were censored on 30 November 2008. If the next date of appointment fell after or within 1 month before the censor date, these patients were considered retained in care. Patients who transferred out were those formally transferred out permanently to another treatment facility.

Risk of attrition was determined by crude odds ratios (ORs) and adjusted ORs. Adjusted ORs were determined through multivariate logistic regression. All variables that were significant or of borderline significance in the crude model were included in the multivariate model. Those with a Walds test P value of <0.15 were kept in the model. Others were maintained in the model if removing them resulted in a change of >15% in the odds ratio of variables. A backward stepwise elimination approach was used until all remaining variables in the model were significant and this was then reported. All related P-values were based on the Walds test. Data analysis was performed using the STATA 8.2 software (Stata corporation, College Station, Texas 77845, USA).

Ethical approval

Ethical approval was received from the MSF and UNION Ethics Review Boards (ERB). The MSF ERB is instituted independently of MSF. The project in Kibera functions under the framework of formal collaborative agreements with the Kenyan Ministry of Health. The data in this study did not include patient identifiers, and all data used in this report constitute what is routinely collected under national management guidelines for TB and ART. General measures are provided in the Kibera facilities to ensure patient confidentiality, consent for HIV testing, and counselling and support for those who receive a positive HIV test result.

Results

Characteristics of the study population

Between January 2005 and November 2008, 2718 ART eligible adults were registered at the ART sites in Kibera; 247 (9%) had no next appointment date specified in the database and were thus excluded from the analysis. Table 1 shows the case registration characteristics of the 2471 adults included in the study. There were 1532 (62%) women, and the median age for all patients was 33 years [Inter-quartile range (IQR), 28–39 years]. The most common opportunistic infection was Pulmonary TB (PTB) (11%).

Table 1 Baseline registration characteristics of ART eligible adults in Kibera (n = 2471)

Variable	n (%)
Total	2471
Sex	
Female	1532 (62)
Male	939 (38)
Age (years)	
15–34	1488 (60)
≥35	983 (40)
Median, years (IQR)	33 (28–39)
WHO clinical stage	
Stage I or II with CD4 <200 cells/μl	551 (22)
Stage III	1439 (58)
Stage IV	481 (19)
BMI (kg/m^2)	
<16	173 (7)
16–16.9	148 (6)
17–18.4	315 (13)
≥18.5	1091 (44)
Unknown	744 (30)
Opportunistic disease	
None	1454 (58)
Weight loss	99 (4)
Herpes zoster	32 (1)
URTI	80 (3)
Papular pruritic eruption	27 (1)
Unexplained diarrhoea	53 (2)
Prolonged unexplained fever (>1 month)	51 (2)
Prolonged oral candida/Oesophageal candidiasis	104 (4)
Pulmonary TB	276 (11)
EPTB	52 (2)
Severe bacterial pneumonia	129 (5)
Severe bacterial infection	50 (2)
Wasting syndrome	23 (1)
Kaposi sarcoma	23 (1)
Others: Angular cheilitis, Seborrheic dermatitis, cryptococcosis extrapulmonary, toxoplasmosis	18 (1)

ART, antiretroviral therapy; IQR, Inter-quartile range; WHO, World Health Organisation; BMI, Body mass index; URTI, Upper Respiratory Tract Infection; TB, Tuberculosis, PTB, Pulmonary TB; EPTB, Extra-pulmonary TB.

Demographic characteristics and opportunistic diseases associated with attrition during ART preparation

Out of 2471 ART eligible adults, 446 (18%, 95% CI: 17–20%) were lost to attrition before starting ART. Loss to follow-up constituted the largest part of this attrition (85%). Median time to attrition was 1.1 months (IQR, 0.5–3.1 months, overall range 1 day – 37 months). Table 2 shows the demographic characteristics and opportunistic diseases associated with attrition pre-ART. Age <35 years (OR 1.4, 95%CI 1.1–1.8), severe malnutrition (OR 1.5, 95%CI 1.1–2.0), active pulmonary tuberculosis (OR 1.6, 95%CI 1.1–2.4), severe bacterial infections (including severe bacterial pneumonia) (OR 1.9, 95%CI 1.2–2.8), and prolonged unexplained fever (for more than 1 month), (OR 2.6, 95%CI 1.3–5.2) were significantly associated with pre-ART attrition.

Discussion

Younger age (<35 years) and life-threatening opportunistic diseases were associated with attrition (deaths and loss to follow-up) among ART eligible patients in pre-ART in an urban slum setting in Kenya. Although overall attrition of 18% pre-ART may be deemed acceptable, we believe that addressing early attrition is important for improving overall programme outcomes and raising the credibility of ART programmes.

The strengths of this study are that a large number of patients were studied, outcomes were available for most patients and, as the data comes from a programme setting, findings likely reflect the operational reality on the ground. The limitations are that the exact cause(s) of attrition (particularly deaths) could not be determined and thus attributed cause(s) might be inaccurate, we may have overestimated attrition as some patients declared lost to follow-up might include silent undeclared transfers out to other health facilities, and patients declared lost to follow-up may include unascertained deaths. In relation to the latter, as attrition was significantly associated with life-threatening opportunistic diseases, a large undefined proportion of those declared lost to follow-up might actually be unascertained deaths, especially as no active tracing systems were in place to trace these patients during the pre-ART phase. This belief is also supported by recent studies from South Africa and Uganda showing that considerable pre-ART attrition is attributable to

Table 2 Demographic and clinical characteristics and opportunistic diseases associated with attrition pre-ART, Kibera, Kenya

Variables	Attrition (%)	OR	Adjusted OR*	*P*-value
Gender				
Female	268/1532 (17)	1		
Male	178/939 (19)	1.1 (0.9–1.4)		
Age (years)				
<35 years	297/1488 (20)	1.4 (1.1–1.7)	1.4 (1.1–1.8)	0.01
≥35 years	149/983 (15)	1		
BMI (kg/m^2)†				
<17	73/321 (23)	1.6 (1.2–2.2)	1.5 (1.1–2.0)	0.02
17–18.4	58/315 (18)	1.2 (0.9–1.7)	1.3 (0.9–1.7)	0.34
≥18.5	171/1091 (16)	1		
Unknown	144/744 (19)	1.3 (1.0–1.6)		
WHO Stage				
Stage 1 & II, CD4 count <200	87/551 (16)	1		
Stage III (CD4 count <350 or no available CD4 count)	263/1439 (18)	1.2 (0.9–1.6)		
Stage IV	96/481 (20)	1.3 (1.0–1.8)		
Year of enrolment				
2005	93/499 (19)	1		
2006	161/704 (23)	1.3 (1.0–1.7)		
2007	93/690 (14)	0.7 (0.5–9.0)		
2008	99/578 (17)	0.9 (0.7–1.2)		
Weight loss				
Absent	427/2372 (18)	1		
Present	19/99 (19)	1.1 (0.6–1.8)		
Pulmonary tuberculosis				
Absent	383/2195 (17)	1	1.6 (1.1–2.4)	0.008
Present	63/276 (23)	1.4 (1.0–1.9)		
Severe bacterial pneumonia/infection				
Absent	397/2292 (17)	1	1.9 (1.2–2.8)	0.004
Present	49/179 (27)	1.8 (1.3–2.5)		
Prolonged unexplained fever				
Absent	428/2420 (18)	1	2.6 (1.3–5.2)	0.008
Present	18/51 (35)	2.5 (1.4–4.6)		

ART, antiretroviral therapy; OR, odds ratio; WHO, World Health Organisation; BMI, body mass index.
*Adjusted odds ratios are only presented for variables included in the multivariate model.
$^\dagger\chi^2$ test for trend = 7.99, P = 0.005.

death (Amuron *et al.* 2009; Fox *et al.* 2010; Ingle *et al.* 2010b).

Attrition tended to occur early on in the pre-ART phase. Possible reasons for this include the following: delayed presentation of patients and thus advanced HIV/AIDS disease, delays in ART initiation resulting in long waiting times and life-threatening HIV-related opportunistic disease (such as diagnosed or covert PTB) or complications such as septicaemia and bacteraemia. Programmatically, this baseline situation is usually ignored because routine cohort reporting of adverse outcomes (deaths and losses to follow-up) is traditionally restricted to registered patients on ART, and thus, the problem of pre-ART attrition remains unnoticed at programme level (Van Griensven *et al.* 2010; Zachariah *et al.* 2010). As a consequence, existing patient tracing systems are not deployed for the benefit of this patient sub-group. As programmes only act on problems apparent in their reporting, our findings suggest that measures need to be implemented to include all 'ART eligible patients into routine cohort reporting and not just those who 'start ART'.

Being relatively younger was associated with higher attrition in the pre-ART phase. This may be linked to younger patients still feeling relatively well at registration and not perceiving the need to return for treatment. As most workers in Kibera are casual workers, they might also have found it difficult to cope with the formalities linked to ART preparation, while trying to find and keep work. These people may well wait until they become more ill before seeking ART care. This merits specific investigation

and probably targeted education and counselling (Braitstein *et al.* 2006).

A particularly interesting finding was that active PTB, severe malnutrition, prolonged unexplained fever (>1 month) and severe bacterial infections were all significantly associated with pre-ART attrition. Ways forward in addressing these challenges are thus needed. Attrition was seen in about one in four PTB patients in the pre-ART phase. Possible reasons could be (i) time constraints and difficulties related to having to access joint TB treatment and ART (with each started at different times as recommended), (ii) patients feeling better after starting TB treatment and deciding to postpone ART initiation, (iii) shortcomings in TB-HIV collaboration, and (iv) unascertained deaths caused by TB. We believe that the latter may contribute most to the pre-ART attrition observed as TB is a leading cause of early deaths among HIV-positive patients (Lawn *et al.* 2005, 2008; Etard *et al.* 2006). Recent WHO guidelines recommending earlier ART initiation among all HIV-positive TB patients, irrespective of CD4 count, should simplify the process of ART initiation.

Severe malnutrition, prolonged unexplained fever (>1 month) and severe bacterial infections were all associated with attrition, and like PTB, we believe that unascertained deaths may contribute to the majority of this attrition. For instance, severe malnutrition, by further compromising host immunity, could predispose to life-threatening superadded infections, increasing the risk of death. Severe wasting, unexplained fever and severe bacterial pneumonia (Scott *et al.* 2000) may be proxy signs of undiagnosed or 'occult' TB, including disseminated TB (Lucas *et al.* 1994; Grant *et al.* 1997; Anglaret *et al.* 2002). As such it may be desirable for patients with severe malnutrition and unexplained fever to undergo more 'intensified' screening for TB, including clinical questioning about cough for more than 2 weeks, sputum examination (including, where feasible, sputum cultures), chest X-ray and abdominal ultrasound for enlarged mesenteric glands. There is some evidence that the only indication of TB in a proportion of such patients might be a positive blood culture but such an investigation remains beyond the reach of most health facilities in resource-limited settings. This highlights the need for development and access to better point-of-care TB diagnostics for such settings. The recently described Xpert MTB/RIF automated molecular test for *Mycobacterium tuberculosis* is a step in the right direction in this regard (Boehme *et al.* 2010). The importance of malnutrition and severe blood-stream infections in HIV-I infected patients in sub-Saharan Africa has been described, the most frequently incriminated strains being non-typhi *Salmonella*, *Streptococcus pneumoniae*, *Escherichia coli* and *Shigella* sp. (Gilks *et al.* 1990; Janoof *et al.* 1992; Grant *et al.* 1997; Gilks 1998; Jones *et al.* 1998; Anglaret *et al.* 2002). Blood culture studies in such patients would be useful to determine the relative contributions of these pathogens and to determine whether routine, empirical antibiotic therapy might be justified.

Finally, the pre-ART attrition observed among ART eligible patients in Kibera was not as high as has been reported in other settings such as South Africa and Uganda (Amuron *et al.* 2009; Larson *et al.* 2010). MSF has supported the MOH-run primary care clinics in Kibera for some years now and its presence and the additional financial, logistic and human resources that the organisation brings to its disposal may explain these lower attrition rates. In other public health facilities that do not have the additional resources and support from an NGO, one might expect this pre-ART attrition to be higher.

In conclusion, in an urban slum setting in Nairobi, a number of clinical markers routinely collected and recorded during preparation for ART were associated with a high risk of pre-ART attrition. These variables could serve as pointers or screening tools to identify patients who merit fast-tracking onto ART and much closer clinical attention.

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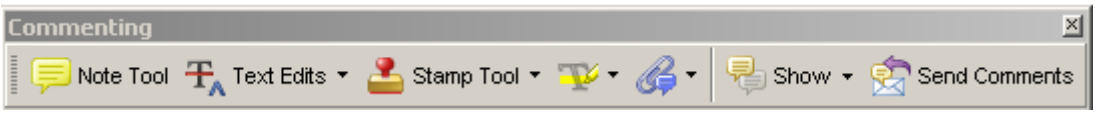

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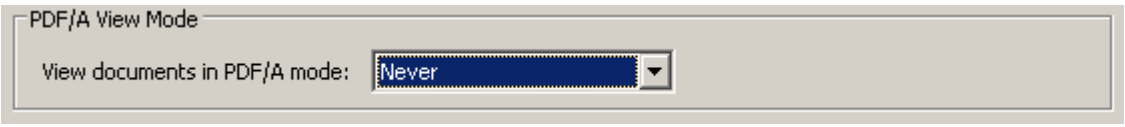

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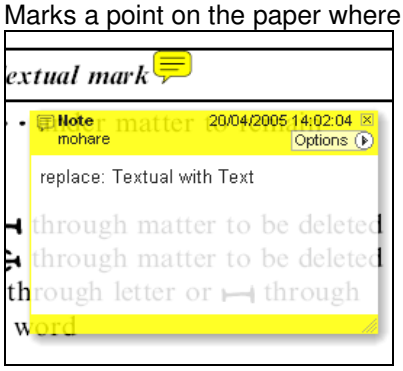

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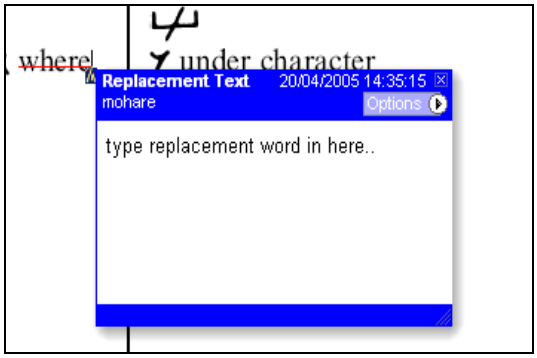

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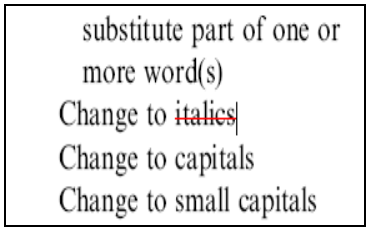

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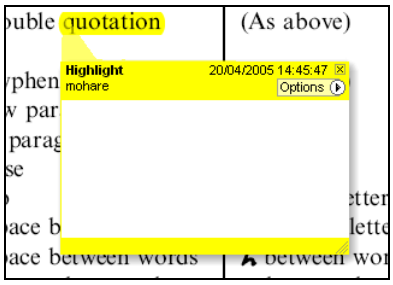
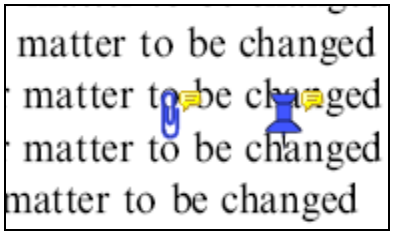


How to use it:

1. Select Highlighter Tool from the commenting toolbar
2. Highlight the desired text
3. Add a note detailing the required change

Attach File Tool — For inserting large amounts of text or replacement figures as a files.

Inserts symbol and speech bubble where a file has been inserted.

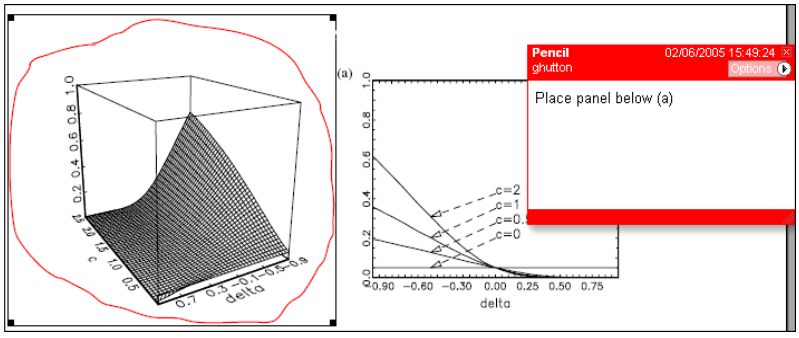


How to use it:

1. Click on paperclip icon in the commenting toolbar
2. Click where you want to insert the attachment
3. Select the saved file from your PC/network
4. Select appearance of icon (paperclip, graph, attachment or tag) and close

Pencil tool — For circling parts of figures or making freeform marks

Creates freeform shapes with a pencil tool. Particularly with graphics within the proof it may be useful to use the Drawing Markups toolbar. These tools allow you to draw circles, lines and comment on these marks.



How to use it:

1. Select Tools > Drawing Markups > Pencil Tool
2. Draw with the cursor
3. Multiple pieces of pencil annotation can be grouped together
4. Once finished, move the cursor over the shape until an arrowhead appears and right click
5. Select Open Pop-Up Note and type in a details of required change
6. Click the X in the top right hand corner of the note box to close.

Help

For further information on how to annotate proofs click on the Help button to activate a list of instructions: