

Lessons from the field

True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi

Joseph Kwong-Leung Yu,^{a,b} Solomon Chih-Cheng Chen,^b Kuo-Yang Wang,^b Chao-Sung Chang,^b Simon D Makombe,^c Erik J Schouten^c & Anthony D Harries^c

Problem In many resource-poor countries that are scaling up antiretroviral therapy (ART), 5–25% of patients are reported as "lost to follow-up". This figure is 9% in Malawi. There is no published information about the true outcome status of these patients.

Approach In four facilities in northern Malawi, ART registers and master cards were used to identify patients who had not attended the facility for 3 months or more and were thus registered as "lost to follow-up". Clinic staff attempted to trace these patients and ascertain their true outcome status.

Local setting Of 253 patients identified as "lost to follow-up", 127 (50%) were dead, 58% of these having died within 3 months of their last clinic visit. Of the 58 patients (23%) found to be alive, 21 were still receiving ART and 37 had stopped treatment (high transport costs being the main reason for 13 patients). Sixty-eight patients (27%) could not be traced, most commonly because of an incorrect address in the register. Fewer patients were alive and more patients could not be traced from the central hospital compared with the peripheral hospitals.

Relevant changes Better documentation of patients' addresses and prompt follow-up of patients who are late for their appointments are required.

Lessons learned ART clinics in resource-poor countries should ensure that patients' addresses are correct and comprehensive. Clinics should also undertake contact tracing as soon as possible in the event of non-attendance, consider facilitating access to ART clinics and take loss to follow-up into consideration when assessing death rates.

Bulletin of the World Health Organization 2007;85:550–554.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Many resource-poor countries with HIV epidemics are scaling up antiretroviral therapy (ART). By December 2005, an estimated 1.3 million people from low- and middle-income countries had been placed on treatment; 810 000 of these were in sub-Saharan Africa.¹ Treatment outcomes reported from various clinics in sub-Saharan Africa, Haiti, Asia and South America have been good, comparable with those observed in countries with higher incomes.^{2–7} Patient outcomes are usually categorized as patients alive and on treatment, stopped treatment, transferred to another facility, dead or "lost to follow-up". Depending on the facility, patients are classified as lost to follow-up if they have missed two or more consecutive clinic appointments²

or have not been seen for at least 2 or 3 months.^{4–6} The proportion of patients lost to follow-up differs between clinics, ranging from 5% in programmes supported by Médecins Sans Frontières⁵ to 25% in western Kenya.⁴ In 18 ART-delivery programmes in Africa, Asia and South America, 15% of 4810 patients were lost to follow-up in the first year of ART, with the average being 12% in programmes with active follow-up and 19% in those with no active follow-up.⁷ To our knowledge, there are no published data from resource-poor countries on the true outcome status of these patients.

Malawi – a small resource-poor country in southern Africa – has been engaged in ART scale-up for nearly 3 years. By 31 March 2006, 46 702 patients had ever started receiving ART

in 66 facilities in the public sector; of these, 33 891 (73%) were registered as alive, 5131 (11%) were dead, 4226 (9%) were lost to follow-up, 3140 (7%) had transferred to another facility and 314 (1%) had stopped therapy.⁸ We hypothesized that many patients lost to follow-up may have died, and therefore conducted a study in northern Malawi to investigate this problem.

Methods

Details on the delivery and monitoring of ART in Malawi have been described previously.⁹ When patients start ART, their details are entered on master cards and an ART register. Patients attend the ART clinic each month, at which time their outcome status is entered on the master card and they are given

^a Taiwan Medical Mission to Malawi, Mzuzu Central Hospital, Mzuzu, Malawi.

^b International Medical Cooperation and Development Center, Pingtung Christian Hospital, Pingtung, Taiwan, China.

^c Clinical HIV Unit, Ministry of Health, PO Box 30377, Lilongwe, Malawi. Correspondence to Anthony D Harries (e-mail adharries@malawi.net).

doi: 10.2471/BLT.06.037739

(Submitted: 17 October 2006 – Final revised version received: 1 February 2007 – Accepted: 2 February 2007)

another month's supply of ART drugs. If a patient is not seen in the clinic for three consecutive months, the patient is registered as a "defaulter" (an abbreviated term for "lost to follow-up") on the master card and also on the register.

Four public-sector ART facilities in the northern region of Malawi were selected for the study. These included one central hospital and three peripheral hospitals (two district hospitals and one mission hospital). Provision of free ART was initiated at the central and mission hospitals in July 2004, and at the two district hospitals in January and June 2005 respectively. For the period between the date when each facility started to provide free ART and 31 March 2006, we identified all patients indicated on the master cards and registers as a defaulter. Using contact details, ART facility staff visited the patients' homes to try to ascertain their true outcome status. If patients were traced to the home, they were asked whether they were still taking ART and if not, why they had stopped. If the patient had died, the relatives were asked when the patient had died. If the patient had moved away, relatives or friends were asked when they had moved.

Ethical approval for the study was granted by the Malawi National Health Sciences Research Committee. Informed

consent was obtained from patients being interviewed, and staff took care not to disclose that the patient was receiving ART when interviewing relatives or friends in the event of the patient's death or transfer.

Data were collected on structured forms, and analysis was carried out using Epi Info version 6.0. Patients from the central and the peripheral hospitals were compared: the χ^2 test with relative risks (RR) and 95% confidence intervals (CI) were used for characteristics and outcomes, and the student's *t*-test was used for time periods between start of ART, default and patient tracing, with differences at the level of 0.05 being regarded as significant.

Results

During the period of observation, 5009 patients were registered as ever having started ART in the four hospitals. Of these, 253 (5%) were registered as defaulters. Table 1 shows patient characteristics, reasons for starting ART, treatment regimens, results of defaulter tracing and time periods between start of ART, date of default and date of patient tracing.

For all defaulters, the median time between start of ART and date of default was 4.3 months, and between date of

default and home visits was 6.4 months. Overall, the commonest reason for default was death, this being the case for 50% of patients. Of those who died, 57% died within 3 months of their last clinic attendance, the median time between start of ART and death being 2.9 (range, 0.1–19.2) months. Fifty-eight (23%) patients were still alive; about one-third had transferred themselves to another ART clinic without informing the clinic where they were registered and about two-thirds had stopped therapy. Of the patients who had stopped ART, reasons included the high cost of transport to the clinic (13 patients; 35%), religious beliefs (4 patients; 11%), persuasion by relatives to stop ART (4 patients; 11%) and other reasons (16 patients; 43%). The remaining 68 patients (27%) could not be traced, most frequently because of an incorrect address in the ART register. The median time between default and home visits was 1.8 (range, 0.1–16) months for patients who were found to be still alive and 4.8 (range, 0.1–18.3) months for patients who could not be traced, a highly significant difference ($P < 0.001$).

The characteristics of patients from the central and peripheral hospitals were similar, except that there were significantly more female defaulters in

Table 1. Characteristics and true outcome status of patients on ART who were classified as "lost to follow-up" from four hospitals in Malawi

| Characteristics and outcome status | All hospitals | Central hospital | Three peripheral hospitals |
|---|-------------------|-------------------|----------------------------|
| Number of patients ever started on ART | 5009 | 3158 | 1851 |
| Female patients | 2985 (60%) | 1854 (59%) | 1131 (61%) |
| Children (aged < 15 years) | 403 (8%) | 371 (12%) | 32 (2%) |
| Number of patients who defaulted | 253 (5%) | 126 (4%) | 127 (7%) |
| Median (range) time between starting ART and diagnosis of default in months | 4.3 (2.6–24.6) | 3.7 (2.9–19.5) | 4.5 (2.6–24.6) |
| Median (range) time between diagnosis of default and home visits in months | 6.4 (0.1–18.3) | 8.2 (0.1–18.3) | 5.1 (0.1–15.6) |
| Characteristics of defaulting patients: | | | |
| Median age (years) | 35 | 35 | 35 |
| Female patients | 151 (60%) | 67 (53%) | 84 (66%) |
| Children (aged < 15 years) | 6 (2%) | 4 (3%) | 2 (2%) |
| Indication for ART: | | | |
| WHO clinical stage 3 | 172 (68%) | 87 (69%) | 85 (67%) |
| WHO clinical stage 4 | 72 (28%) | 31 (25%) | 41 (32%) |
| WHO clinical stage 1 or 2 with a CD4 count < 250 per mm ³ | 9 (4%) | 8 (6%) | 1 (1%) |
| ART regimen: | | | |
| First-line regimen ^a | 250 (99%) | 124 (98%) | 126 (99%) |
| Alternative first-line regimen ^b | 3 (1%) | 2 (2%) | 1 (1%) |

(Table 1, cont.)

| Characteristics and outcome status | All hospitals | Central hospital | Three peripheral hospitals |
|--|---------------|------------------|----------------------------|
| True outcome status at the default tracing visit: | | | |
| Total alive | 58 (23%) | 18 (14%) | 40 (32%) |
| Status of patients found to be alive: | | | |
| Alive on ART at the same clinic ^c | 1 (2%) | 0 (0%) | 1 (3%) |
| Alive on ART at a different clinic ^d | 20 (34%) | 9 (50%) | 11 (28%) |
| Alive but had stopped ART | 37 (64%) | 9 (50%) | 28 (69%) |
| Dead | 127 (50%) | 58 (46%) | 69 (54%) |
| Time of death after last ART attendance: | | | |
| Month 1 | 30 (24%) | 15 (26%) | 15 (22%) |
| Month 2 | 29 (23%) | 15 (26%) | 14 (20%) |
| Month 3 | 14 (11%) | 5 (9%) | 9 (13%) |
| Month 4 and beyond | 54 (42%) | 23 (39%) | 31 (45%) |
| Lost to follow-up | 68 (27%) | 50 (40%) | 18 (14%) |
| Reasons for unsuccessful tracing: | | | |
| Incorrect address in ART register | 55 (81%) | 42 (84%) | 13 (72%) |
| Patient moved and family remained | 7 (10%) | 4 (8%) | 3 (17%) |
| Patient and family moved | 6 (9%) | 4 (8%) | 2 (11%) |

ART, antiretroviral therapy.

^a Fixed drug combination of stavudine, lamivudine and nevirapine.

^b Drug regimen where zidovudine is substituted for stavudine in case of peripheral neuropathy, or efavirenz for nevirapine in case of hepatitis or severe cutaneous reaction.

^c Patient came late for appointment and did not disclose to ART clinic staff that he/she was already registered for treatment.

^d Patients transferred to other ART clinics without informing the staff from the clinic where they had first been registered.

peripheral than in central hospitals ($P < 0.05$). The time between default and home visits was significantly longer for patients from central hospitals than for patients from peripheral hospitals ($P < 0.001$). Significantly fewer patients from central hospitals were found alive (RR, 0.45; 95% CI, 0.28–0.75; $P < 0.01$) and significantly more patients from central hospitals could not be traced (RR, 2.80; 95% CI, 1.7–4.1; $P < 0.001$) compared with patients from peripheral hospitals. There were no significant differences in the reasons for stopping ART or for continued loss to follow-up between the two groups.

Discussion

This study shows that half of the patients receiving ART who were subsequently lost to follow-up were dead, with a large proportion dying soon after they failed to attend the clinic. The reasons for death were not ascertained. About one-quarter of patients were alive, some having transferred to another facility and some deciding to stop therapy. An important reason for stopping therapy was the cost of transport from homes to clinics. The remaining patients could not be traced, with an incorrect address in the register being the most common reason. Whether patients gave a wrong

address or whether the details obtained by clinic staff were insufficient is unclear. These overall outcomes are similar in many respects to those found several years ago in Malawi in a study in patients registered as defaulters with regard to treatment for tuberculosis.¹⁰

There were some differences between the central and peripheral hospitals in terms of the characteristics of defaulters. A higher proportion of women from the peripheral hospitals were defaulters. Although part of the explanation may be that peripheral hospitals registered slightly more women to receive ART, other factors may be responsible and this requires further study. The rate of failure to trace patients was higher for

patients from the central hospital, and this may relate to the longer period of time between default and the home visit and the general difficulties faced in tracing mobile patients in a congested urban environment.

There are several important lessons to be learnt from this study (Box 1). First, ART clinics need to ensure that the address recorded for the patient is correct in order to facilitate contact tracing if this becomes necessary. Second, provided that resources are available, clinics should attempt to trace patients who stop attending the clinic in order to bring patients back to therapy. This needs to be done as soon as possible, as the longer the delay the more likely

Box 1. Lessons learned

- An operational research study in northern Malawi found that the reasons for being “lost to follow-up” for patients started on antiretroviral therapy (ART) were: death, 50%; alive and on ART, mainly at another clinic, 8%; alive and stopped therapy, 15%; and unable to be traced, 27%. The commonest reason for remaining patients being “lost to follow-up” was an incorrect address in the ART register.
- ART clinics need to record correct and comprehensive addresses, and should try to do contact tracing as soon as possible in the event of clinic non-attendance. Clinics also should consider facilitating better access to care for those with transport difficulties.
- True outcome status may differ depending on whether the ART clinic is in an urban or rural environment.
- In any comparison of treatment outcomes between clinics, particularly with regard to death rates, the issue of patient loss to follow-up cannot be ignored.

it is that the patient will be untraceable. Third, ART programmes need to consider the plight of those who have difficulty accessing ART clinics, and either try to site new ART clinics in better locations, set up outreach clinics or look into ways of financially supporting patients' transport to clinics. Fourth, there may be differences in outcomes between patients who have defaulted from central urban hospitals compared with those from more peripheral rural hospitals, and ART programmes should determine local causes of loss to follow-

up. Finally, country and clinic reports on treatment outcomes must take the issue of loss to follow-up into consideration, particularly with regard to death rates. ■

Acknowledgements

The Taiwan Medical Mission to Malawi is sponsored by the Taiwan International Cooperation and Development Foundation and managed by Pingtung Christian Hospital, Taiwan, China. The Taiwan Medical Mission is based in Mzuzu Central Hospital in northern Malawi,

and is cooperating with staff, peripheral hospitals and Malawi's health ministry to fight HIV and AIDS.

Anthony D Harries is supported by Family Health International, USA, and has an honorary position at the London School of Hygiene and Tropical Medicine. Erik J Schouten is supported by Management Sciences for Health, USA. An anonymous donor provided funds to support the active tracing of patients to their homes.

Competing interests: None declared.

Résumé

Véritables issues du traitement antirétroviral pour les patients considérés comme « perdus de vue » au Malawi

Problématique Dans nombre de pays à revenu modeste qui ont entrepris d'étendre le traitement antirétroviral (ART), 5 à 25 % des patients sont signalés comme « perdus de vue ». Ce chiffre est de 9 % pour le Malawi. On ne dispose pas de données publiées sur la véritable issue pour ces patients.

Démarche Dans quatre établissements de la partie nord du Malawi, on a utilisé les livres-registres de délivrance des ART et les cartes maîtresses pour identifier les patients ne s'étant pas rendu dans l'établissement depuis 3 mois ou plus et enregistrés ainsi comme « perdus de vue ». Le personnel clinique s'est attaché à retrouver la trace de ces patients et à déterminer l'issue véritable du traitement dans leur cas.

Contexte local Sur 253 patients classés comme « perdus de vue », 127 (50 %) étaient morts et parmi ces patients décédés, 58 % avaient perdu la vie dans les 3 mois suivant leur dernière visite au dispensaire. Parmi les 58 patients retrouvés en vie (23 %), 21 prenaient encore des antirétroviraux et 37 avaient interrompu leur traitement (les coûts excessif du transport étant la

principale raison de cet arrêt pour 13 d'entre eux). Soixante-huit patients (27 %) n'ont pu être retrouvés, le plus souvent à cause de l'inexactitude de l'adresse enregistrée dans leur dossier. Peu des patients perdus de vue étaient encore en vie et le nombre des patients impossibles à retrouver était plus important pour l'hôpital central que pour les établissements périphériques.

Modifications pertinentes Il convient de relever avec plus de rigueur l'adresse des patients et d'entreprendre rapidement un suivi de ceux qui tardent à se présenter aux rendez-vous.

Enseignements tirés Les établissements délivrant les traitements ART dans les pays à faible revenu doivent s'assurer de l'exactitude et de la complétude de l'adresse qu'ils enregistrent pour leurs patients. Ils doivent aussi entreprendre dès que possible une recherche des contacts si un patient ne se présente plus aux rendez-vous, envisager de faciliter l'accès au lieu de délivrance du traitement ART et prendre en compte les « perdus de vue » dans l'évaluation des taux de mortalité.

Resumen

Evolución real de los pacientes sometidos a terapia antirretroviral y perdidos en el seguimiento en Malawi

Problema En muchos países con recursos escasos que están extendiendo masivamente la terapia antirretroviral (TAR) se informa de que un 5%-25% de los pacientes tratados se pierden en el seguimiento. En Malawi el porcentaje es del 9%. No hay datos publicados sobre la verdadera evolución de esos pacientes.

Métodos En cuatro establecimientos del norte de Malawi, se utilizaron los registros de TAR y las tarjetas maestras para identificar a los pacientes que no habían acudido al establecimiento durante 3 o más meses y estaban registrados por tanto como «perdidos en el seguimiento». Trabajadores de esos centros intentaron localizar a los pacientes y evaluar su estado de salud real.

Contexto local De 253 pacientes identificados como «perdidos en el seguimiento», 127 (50%) habían muerto, el 58% de ellos en los 3 meses siguientes a su última visita al consultorio. De los 58 pacientes (23%) hallados con vida, 21 seguían recibiendo TAR y 37 habían interrumpido el tratamiento (13 de ellos

adujeron como causa principal el alto precio de los transportes). Sesenta y ocho pacientes (27%) no pudieron ser localizados, fundamentalmente porque en los registros figuraba una dirección incorrecta. En comparación con los hospitales periféricos, en el caso del hospital central había menos pacientes vivos y más a los que no se pudo localizar.

Cambios destacables Es necesario registrar mejor las direcciones de los pacientes y reanudar rápidamente el seguimiento de los que faltan a las citas concertadas.

Enseñanzas resultantes Los consultorios de TAR de los países de recursos escasos deben procurar que las direcciones de sus pacientes se registren correctamente y sin omisiones. Los consultorios deben adoptar además lo antes posible medidas de localización de contactos en caso de no asistencia, estudiar la manera de facilitar el acceso a los consultorios de TAR, y tener en cuenta las pérdidas en el seguimiento a la hora de evaluar las tasas de mortalidad.

ملخص

المآل الحقيقي للمرضى المنقطعين عن المتابعة في المعالجة بالأدوية المضادة للفيروسات القهقرية في مالابوي

هي السبب الرئيسي لذلك عند 13 مريضاً منهم). ولم يمكن اقتفاء أثر 68 مريضاً (27%)، وأكثر الأسباب شيوعاً لذلك هو عدم صحة العنوان المسجل في السجلات والبطاقات. ويبدو أن العدد في المستشفيات المركزية أقل بالنسبة للمرضى الذين بقوا على قيد الحياة، وأنه أكثر بالنسبة لمن تعذر اقتفاء أثره بالمقارنة مع ما هو عليه في المستشفيات المحيطة. التغييرات الملائمة: ينبغي تحسين توثيق عناوين المرضى ومتابعتهم قوَر تأخرهم عن الحضور في مواعيدهم. الدروس المستفادة: ينبغي على عيادات المعالجة بالأدوية المضادة للفيروسات القهقرية تسجيل عناوين صحيحة ومستوفاة للمرضى لديها. وينبغي أن تقتفي أثر المرضى قوَر تغيُّبهم عن الحضور، وأن تتوخى التسهيل لإتاحة المعالجة بالأدوية المضادة للفيروسات القهقرية في العيادات المخصصة لذلك، مع أخذ فقدان المتابعة في الحسبان عند تقييم معدلات الوفيات.

المشكلة: في معظم البلدان الفقيرة بالموارد التي تنهض بالمعالجة المضادة للفيروسات القهقرية، يرد في التقارير أن 5-22% من المرضى قد انقطعت متابعتهم. وفي مالابوي يشكّل هؤلاء 9%. ولا يوجد معلومات منشورة عن المآل الحقيقي لهؤلاء المرضى. الأسلوب: في 4 مرافق تقع شمال مالابوي، تستخدم السجلات والبطاقات للتعرف على المرضى الذين لا يزورون المرفق الصحي لمدة 3 شهور أو أكثر، ويسجّلون نتيجة لذلك من المنقطعين عن المتابعة. ويحاول العاملون السريريون اقتفاء أثر هؤلاء المرضى والتعرف على أوضاعهم ومآلهم الحقيقي. الموقع المحلي: تبين أن عدد المنقطعين عن المتابعة 253 مريضاً، وأنه قد مات منهم 127 (50%)، وأن 58% من هؤلاء الموتى ماتوا خلال الأشهر الثلاثة التي تلت زيارتهم الأخيرة. فيما وجد أن 58 مريضاً (23%) لا يزالون أحياء، وأن 21 منهم لا يزال يتلقّى المعالجة بالأدوية المضادة للفيروسات القهقرية، فيما أوقف 37 منهم المعالجة (وقد كانت التكاليف المرتفعة لوسائل النقل

References

1. Progress on global access to HIV antiretroviral therapy: a report on '3 by 5' and beyond, March 2006. Geneva: WHO; 2006.
2. Wester CW, Kim S, Bussmann H, Avalos A, Ndwapu N, Peter TF, et al. Initial response to highly active antiretroviral therapy in HIV-1C-infected adults in a public sector treatment program in Botswana. *J Acquir Immune Defic Syndr* 2005;40:336-43.
3. Severe P, Leger P, Macarthur C, Noel F, Bonhomme G, Bois G, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med* 2005;353:2325-34.
4. Wools-Kaloustian K, Kimaiyo S, Diero L, Siika A, Sidle J, Yiannoutsos CT, et al. Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from Western Kenya. *AIDS* 2006;20:41-8.
5. Calmy A, Pinoges L, Szumilin E, Zachariah R, Ford N, Ferradini L on behalf of Médecins Sans Frontières. Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort. *AIDS* 2006;20:1163-9.
6. Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambho L, et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. *Lancet* 2006;367:1335-42.
7. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boule A, Miotti P, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006; 367:817-24.
8. ARV therapy in Malawi – up to 31st March 2006. Quarterly report. Malawi: HIV Unit, Ministry of Health; 2006.
9. Libamba E, Makombe S, Harries AD, Chimzizi R, Salaniponi FM, Schouten EJ, et al. Scaling up antiretroviral therapy in Africa: learning from tuberculosis control programmes – the case of Malawi. *Int J Tuberc Lung Dis* 2005; 9:1062-71.
10. Kruyt ML, Kruyt ND, Boeree MJ, Harries AD, Salaniponi FM, van Noord PA. True status of smear-positive pulmonary tuberculosis defaulters in Malawi. *Bull World Health Organ* 1999;77:386-91.