



ORIGINAL ARTICLE

High rate of virological re-suppression among patients failing second-line antiretroviral therapy following enhanced adherence support: A model of care in Khayelitsha, South Africa

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Objective. To describe and evaluate the outcomes of a support programme for patients with virological failure while receiving second-line antiretroviral therapy (ART) in South Africa.

Method. We described a comprehensive medical and counselling patient support programme for patients receiving second-line ART and with two consecutive viral loads (VLs) >1 000 copies/ml. Patients with >3 months follow-up and at least one VL measurement after inclusion in the programme were eligible for analysis.

Results. Of 69 patients enrolled in the programme, 40 had at least one follow-up VL and no known drug resistance at enrolment; 27 (68%) of these re-suppressed while remaining on second-line ART following enhanced adherence support. The majority (18/27; 67%) achieved re-suppression within the first 3 months in the programme. Five patients with diagnosed second-line drug resistance achieved viral re-suppression (<400 copies/ml) after being switched to third-line ART. Seven patients (7/40; 18%) did not achieve viral re-suppression after 9 months in the programme: 6 with known adherence problems (4 without drug resistance on genotype) and 1 with a VL <1 000 copies/ml. Overall, 3 patients (4%) died, 3 (4%) were lost to follow-up and 2 (3%) were transferred out.

Conclusion. Our experience from a routine programme demonstrates that with targeted adherence support, the majority of patients who were viraemic while receiving second-line ART returned to an undetectable VL within 3 months. By increasing the time receiving second-line ART and decreasing the need for genotypes and/or third-line ART, this intervention may reduce costs.

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At the end of 2012, 35 million people were estimated to be living with HIV worldwide – most in sub-Saharan Africa.^[1] Antiretroviral therapy (ART) was first introduced in South Africa (SA) through pilot projects in 2001. In 2004, the country launched its public sector ART programme, now the largest ART programme in the world. By mid-2013, approximately 2.5 million people had initiated ART free of charge through the public sector.^[2]

As increasing numbers of patients are enrolled in treatment regimens, there is an increase in the number failing first-line ART and being switched to second-line ART.^[3-6] The durability of second-line regimens is not well-established and there is growing concern in SA and elsewhere regarding the

management of second-line failure, given the high cost of third-line ART and limited treatment options. In one study conducted in Soweto, SA, about one-third of patients receiving the second-line lopinavir/ritonavir (LPV/r)-based regimen were found to be viraemic.^[7] In another study in Khayelitsha, SA, patients receiving second-line ART were less likely to be virologically suppressed than patients remaining on first-line ART at equivalent durations of treatment (odds ratio (OR) 0.51; 95% confidence interval (CI) 0.26 - 1.01).^[8]

North American and European ART guidelines recommend that genotyping governs decisions on the appropriate treatment for patients failing second-line ART.^[9] In Khayelitsha, where routine viral load (VL) testing is available, targeted genotyping and switching to third-line ART has been implemented

in 2011 on the basis of expert advice. The most recent SA ART guidelines, published in 2013, recommend that specialist systems be created within programmes to guide clinical management and access to third-line regimens based on genotype resistance testing and expert opinion.^[10]

Previous studies have found that only a minority of second-line patients with virological failure in the Khayelitsha programme had major protease inhibitor (PI) mutations necessitating third-line ART.^[11] This suggests that the high VL measurements observed may largely be explained by adherence difficulties. In this study, we describe an enhanced patient support programme and short-term outcomes for patients with sustained viraemia on second-line ART regimens in the largest ART site in Khayelitsha.

Methods

Study setting

Khayelitsha sub-district (population ~500 000 inhabitants) is located on the outskirts of Cape Town, SA, and has one of the highest burdens of HIV and tuberculosis (TB) in the country. In 2010, antenatal HIV prevalence was measured at 26%; the TB case-notification rate reached nearly 1 500/100 000 inhabitants, and the TB/HIV co-infection rate was close to 73%.^[12]

The Khayelitsha programme was the first in SA to provide ART at the primary care level in the public sector. The programme was established in 2001 by Médecins Sans Frontières (MSF) and the Provincial Government of the Western Cape (PGWC) and has been described previously.^[8,12,19] MSF's role evolved from the provision of first-line ART to piloting models of primary care for drug-resistant tuberculosis (DR-TB), long-term ART and vulnerable groups such as children, youth, pregnant women and men. By the end of 2011, over 20 000 patients remained in ART care provided by the Department of Health in Khayelitsha.^[12]

Ubuntu Clinic, the study site with the largest and oldest cohort of patients receiving ART in Khayelitsha, had initiated over 6 000 patients on ART, of whom 482 (7%) were receiving second-line PI-based regimens (mainly LPV/r-based) at the time of the study.

The PGWC ART guidelines recommend a first VL measurement four months after ART initiation. Follow-up VL monitoring is recommended 12 months after treatment initiation and annually thereafter. Patients with a VL $\geq 1\ 000$ copies/ml and no medical

reasons for a virological breakthrough receive adherence counselling and a follow-up VL measurement three months later. Virological treatment failure is defined as having two consecutive VLs $\geq 1\ 000$ copies/ml. Such patients are switched to an appropriate second-line LPV/r-based regimen.

Second-line support clinic

Prior to the introduction of the intervention, and as is common in this setting, patients with a detectable VL routinely received at least one adherence session performed by clinic counsellors. These sessions focused on re-educating patients on treatment literacy rather than problem-solving around specific adherence barriers. Clinicians and counsellors often found it challenging and frustrating to deal with patients who were failing treatment and had no further treatment options.

In 2010, MSF partnered with the PGWC to pilot a 'second-line failure clinic' intervention at Ubuntu clinic, targeting patients receiving second-line ART and with two or more consecutive VL measurements $\geq 1\ 000$ copies/ml.

All patients enrolled in the programme were offered a comprehensive package of medical and counselling support (Fig. 1), and were followed up by clinical staff (doctor and/or nurse). Counsellors conducted a simple screen for substance abuse and depression at the enrolment visit and referred patients for additional services accordingly. A typical visit would consist of a medical visit, an individual adherence support session and a group support activity.

Medical visits carried out by a clinician (medical officer or professional nurse) focused on clinical issues relating to treatment failure, such as opportunistic infections, drug interactions, side-effects and possible drug resistance. The clinician also engaged in adherence support and HIV drug resistance tests were only performed when patients failed to obtain virological re-suppression after all adherence barriers were addressed. Individual adherence support sessions were conducted by

counsellors. During these individual sessions, the patient's specific adherence barriers were identified and assistance was provided to problem-solve these issues. During monthly follow-up visits, patients were encouraged to report back on the progress that they had made or the difficulties that they still faced in adhering to treatment. Adherence barriers and plans made were noted in the patient's folder to aid follow-up.

In addition, patients were invited to attend support group sessions facilitated by a counsellor. Grouping patients with similar difficulties encouraged patients to share their barriers and solutions, and also promoted openness and honesty.

After a period of three months in the second-line failure intervention, a VL measurement was repeated. Patients who achieved virological suppression were then referred back to routine clinic care. Patients who did not achieve virological suppression were retained in the intervention and assessed for HIV drug resistance testing.

This intervention ensured that the small number of patients who were struggling on second-line ART were identified, temporarily removed from the normal flow of the clinic, and given enhanced attention and support, which is challenging to offer to all patients in a busy ART clinic.

Outcome evaluation

The primary outcome was virological re-suppression, defined as achieving a VL ≤ 400 copies/ml after having two consecutive VL measurements $\geq 1\ 000$ copies/ml. Patients who had no contact with the clinic for 6 months were regarded as lost to follow-up (LTFU). Those patients who requested transfer to another health facility were considered transferred out (TO). Data for each patient on the date of first-line ART initiation, initiation of second-line therapy, VL measurements and the dates of VL tests were extracted from routinely collected data in the electronic patient register in the clinic. Date of registration in the clinic was

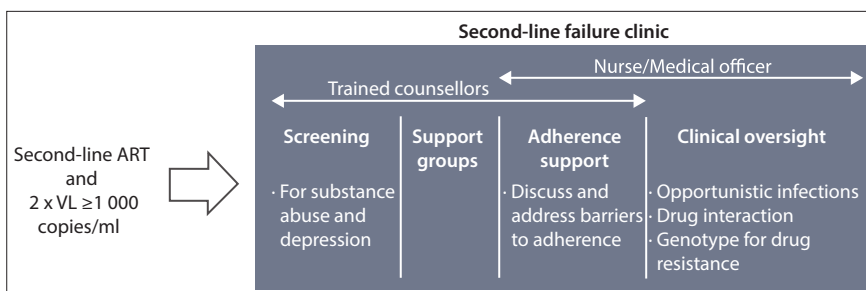


Fig. 1. Key elements of the second-line ART failure clinic. (VL = viral load.)

captured from the paper register used by the doctors to track patients in care. Information regarding barriers to adherence was extracted from counselling notes.

Statistical analysis

Enrolled patients with less than three months of follow-up and patients who did not have a follow-up VL measurement in the programme were excluded from the analysis. We described the treatment and VL history of patients during the study period with frequencies for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. The following variables were included: duration of first-line ART, type of first-line ART, duration (years) receiving first-line ART before the first and second of two consecutive VLs >1 000 copies/ml, duration and choice of second-line treatment, and duration in the second-line failure programme. The analysis of routine cohort data was approved by the University of Cape Town's Research Ethics Committee.

Results

From January to December 2011, a total of 69 patients were enrolled in the programme (Fig. 2); 29 were excluded from the analysis

as they had not had a follow-up VL. Four patients who had known drug resistance at the time of enrolment were also excluded from the analysis. The median duration on first-line treatment was 3.4 years (IQR 2.1 - 4.3). The median duration of the first-line regimen before two consecutive elevated VLs was 1.7 years (IQR 0.9 - 2.5). Once switched to a second-line regimen, the median time to the first detectable VL measurement was 0.7 years (IQR 0.4 - 1.1).

Overall, during 9 months of follow-up, 27 of the remaining 40 patients (68%) achieved virological suppression while remaining on second-line treatment. One patient was switched to third-line ART after genotyping showed PI resistance. Seven patients (18%) continued to experience viraemia, either with known adherence problems or having been genotyped and found to be treatment-sensitive; none of these patients was switched to third-line ART and all continued in the programme. Five patients left the programme due to death, LTFU or TO.

Timing of virological re-suppression

Eighteen out of 40 patients (46%) achieved virological re-suppression within 3 months, 7

(18%) within 6 months, and 2 (5%) within 9 months. One patient underwent genotyping, was found to have PI resistance and was switched to third-line ART, subsequently re-suppressing within 3 months.

After re-suppression, 19% (5/27) of patients experienced a recurrence of viraemia: 3 of the 18 who suppressed at three months, and two of the seven patients who suppressed at six months. Of the seven patients who failed to re-suppress, four were genotyped and found to have a drug-sensitive virus; two had known adherence issues (one due to alcoholism, one for unspecified reasons) and one had a VL of 400 - 1 000 copies/ml, and could therefore not be genotyped.

Obstacles to adherence

The four main obstacles to adherence reported by patients entering the programme were: issues regarding the dosing schedule and not having a fixed routine; ignorance about the need for good adherence; a previous negative experience with clinic staff; and simply forgetting to take the drugs as needed. The action plans to address these barriers were: changing the dosing schedule; treatment education through support groups; specific clinic staff dedicated to patients with treatment failure; and reinforced counselling support.

Discussion

In this routine programme, more than two-thirds of patients failing second-line ART achieved virological re-suppression without changing regimen and following an enhanced patient-support intervention. The majority of patients re-suppressed within three months after enrolment in the programme.

Our findings are important for a number of reasons. Firstly, patients failing second-line ART have limited treatment options available as third-line regimens are extremely costly. In our study population, the median duration of the first-line regimen before two consecutive elevated VLs was 1.7 years and the median time to the first detectable VL measurement after being switched to a second-line regimen was 0.7 years. This suggests that these may be patients with significant barriers to adherence. Remaining on a failing ART regimen without acting on the reasons for treatment failure could compromise the efficacy of future treatment options. Failure rates of second-line therapy are higher than reported rates of failure of first-line therapy.^[13] A systematic review and meta-analysis of treatment outcomes of patients receiving

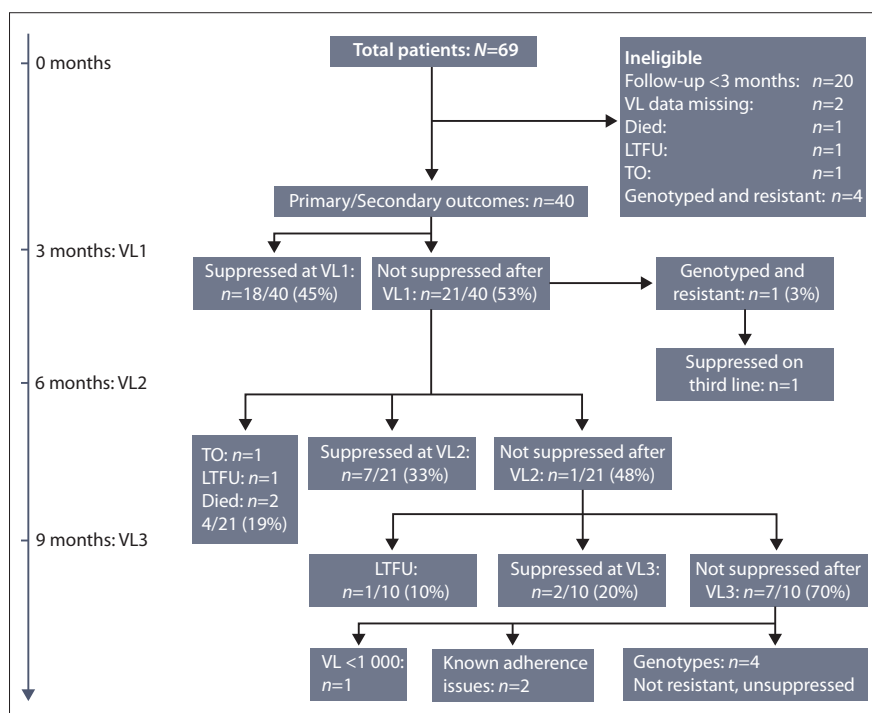


Fig. 2. Flow diagram of outcomes of patients failing second-line antiretroviral therapy enrolled in a comprehensive medical and counselling patient support programme at a primary healthcare clinic, in Khayelitsha, South Africa in 2011. (TO = transfer out; LTFU = loss to follow-up; VL1, VL2, VL3 = first, second and third VL measurements after enrolment into the programme.)

* 3 patients experienced a VL >400 copies/ml at VL2.

** 2 patients experienced a VL >400 copies/ml at VL3.

second-line ART in resource-limited settings found a high proportion with virological failure, with most failures occurring within six months after initiation of second-line therapy.^[14] For long-term health to be maintained in resource-limited settings where treatment options are limited, it is important to maximise the clinical benefits derived from each regimen. This has implications for the wide-scale rollout of ART in SA as well as in other resource-limited settings. The enhanced patient-support programme requires additional resources for a small number of specific patients, but may avoid unnecessary and costly regimen switching. The outcomes of this pilot programme are now informing the implementation of an adherence-support programme for patients at risk of failing first-line therapy.^[15]

Adherence to ART is a key factor for achieving successful treatment outcomes in individual patients and for the success of large-scale ART programmes.^[16] To maintain virological suppression, evidence suggests that individuals are required to take at least 80% of their medication for PI-based therapies,^[17-19] and at least 95% of non-nucleoside-based therapies.^[16] An emerging challenge for large ART programmes is maintaining patient-centred care while enrolment is on-going and total patient numbers are constantly increasing.^[20] Our findings suggest that providing continuity of care for a period of time under the same healthcare staff may promote adherence.

Access to genotyping and third-line regimens remains a major challenge for public sector programmes. As has been reported by a previous study from the same and other programmes,^[21,22] most of the samples genotyped remained susceptible to PIs due to a lack of drug exposure, with adherence problems constituting the major issue. In another study conducted in Khayelitsha,^[11] only two of 37 genotyped samples had major PI mutations. Nevertheless, some second-line virological failures do have major PI mutations that confer resistance and third-line ART will likely become a growing concern. The model of care described here provides an approach to limit the need for costly genotyping by identifying those patients who are non-adherent. In our cohort, only five out of 40 possible samples were genotyped, and 20% of those were found to be resistant. In this way, such a model may be cost-saving.

Five patients experienced virological rebound after VL re-suppression and 18% of all patients did not achieve re-suppression while remaining in the programme. These patients chose to remain in the programme as they experienced continued value in the adherence support received. Adherence problems and/or treatment barriers were identified, highlighting the need for further research on optimal adherence support.

Conclusion

Our findings from an operational setting within routine care are promising, as they demonstrate that patients failing second-line treatment can become adherent with programmatic support. Our study resulted in increased durability of the second-line ART regimen, decreasing the need for costly third-line regimens and preventing many unnecessary genotypes by early identification of, and action on barriers to adherence. While our descriptive study shows satisfactory short-term outcomes, the long-term impact is as yet uncertain and remains to be evaluated.

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