**Clinic-level factors influencing patient outcomes on antiretroviral therapy in primary health clinics in South Africa**

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**Background**

An unprecedented effort by global organizations, governments and health providers has achieved access to antiretroviral treatment (ART) for over 15.8 million individuals infected with the human immune-deficiency virus (HIV) in low- and middle-income countries by June 2015[[1](#_ENREF_1)]. In South Africa, an estimated 3 million people were on ART by June 2015[[2](#_ENREF_2)]. The numbers needing treatment is likely to increase due to the recent change in WHO guidelines[[3](#_ENREF_3)], as well as new evidence that early antiretroviral treatment prevents onward transmission of the virus[[4](#_ENREF_4)].

Treatment programmes face the challenge of maximising retention and maintaining virological suppression for prolonged periods in order to realise the benefits of treatment [[5](#_ENREF_5), [6](#_ENREF_6)]. The shortage of health workers, exacerbated by inadequate supply, inequitable distribution and accelerated migration[[7](#_ENREF_7), [8](#_ENREF_8)], requires an understanding of which factors are most important in achieving good patient outcomes to inform programmatic design.

Most literature has focused on patient-level clinical factors that predict virological outcomes and losses to follow up [[9-12](#_ENREF_9)]. Apart from a few randomised controlled trials looking at a limited number of interventions aimed at improving adherence or retention in patients on ART [[13-16](#_ENREF_13)][[17](#_ENREF_17)], information about which health systems or clinic-level factors influence ART outcomes is limited. Review of qualitative studies revealed the following themes organised according to Lavis and colleagues[[18](#_ENREF_18)]: staffing of the clinic[[19-22](#_ENREF_19)]; the organization of the health system (such as the range of services provided [[23](#_ENREF_23)], waiting times [[24](#_ENREF_24)], inconsistency regarding payments [[24](#_ENREF_24)], provision of social support [[25-27](#_ENREF_25)], follow-up of missed appointments[[22](#_ENREF_22)], and availability of privacy[[28](#_ENREF_28)]); quality of care (such as quality of counselling[[19](#_ENREF_19), [28-31](#_ENREF_28)] and the patient-provider relationship[[23](#_ENREF_23), [25](#_ENREF_25), [27](#_ENREF_27), [29](#_ENREF_29), [32](#_ENREF_32)]); and issues specific to ART (medication costs [[20](#_ENREF_20)], packaging of medication [[33](#_ENREF_33)] and cost of additional medical tests[[20](#_ENREF_20), [33](#_ENREF_33)]).

Clinic issues may be easier to influence than inherent patient characteristics. The aim of this study was to determine which specific clinic-level factors influence ART treatment outcomes, specifically unsuppressed viral load and loss to follow up in individuals on antiretroviral therapy.

**Methods**

***Setting and HIV programme description:*** This observational study was conducted inclinics owned by private practitioners or non-governmental organisations which were part of the Aurum Institute’s HIV treatment programme funded through the President’s Emergency Plan for AIDS Relief (PEPFAR). The programme provided treatment guidelines, clinical support, training of health care workers, site monitoring and a standardised data management system [[1](#_ENREF_1)]. The clinics supported by this programme, ranged from urban sophisticated centres to solo general practitioners in rural towns, as described previously[[34](#_ENREF_34)].

***Clinic and participant selection:***  From participating clinics, adults (>18 years old) who started on ART from 1 January 2006 to 31 December 2009 were included. Data were included to 31 December 2010. Patients who had a previous history of ART were included as these were primarily women who had received ART for prevention of mother to child transmission (PMTCT).

***Treatment guidelines:*** Medical eligibility criteria and treatment guidelines were in line with South African Guidelines for ART initiation in 2006, and these changed in 2010[[35](#_ENREF_35), [36](#_ENREF_36)].

***Programmatic collection of patient data:*** Routine clinical data including demographic and clinical information were collected on standardised forms and entered onto a centrally-managed database. Patient data, identified using unique clinic numbers, were integrated with laboratory records, which included CD4 count and viral load. Patients no longer receiving ART care, for any reason, were reported using deregistration forms. Information on deaths was also ascertained through linkage of the South African identification number to the South African vital statistics registry.

***Additional data collection for this study:*** Data collection tools were designed to collect the most important patient and clinic-level factors that might influence patient outcomes as were identified in previous literature reviews of both qualitative and quantitative studies on adherence, retention and virological suppression. Where possible, data collection tools that had already been used in South Africa were sought and adapted for this study[[37-40](#_ENREF_37)]. Information on clinic characteristics were collected using a clinic assessment tool and an interview with a clinic manager or designee. Care was taken to collect information first-hand (staff training from staff rather than managers) to reduce social desirability bias, and, where possible, to measure clinic attributes directly with facility inspection. In addition, all staff members involved in HIV care at each clinic completed a self-administered questionnaire to measure their own education, motivation and working environment.

To control for differences in patient populations between clinics, data on socio-economic factors, not routinely measured in the programme, were collected from a sample of approximately 40 patients per clinic attending for their routine clinic or ART collection visits*, as a “proxy” for the overall clinic population*. The patient questionnaire also collected information about the patient-provider relationship[[37](#_ENREF_37)] and patient satisfaction. More detailed questions were added later to the questionnaire; these were only implemented in 19 clinics after obtaining approval for a protocol amendment. The questions added were to measure the following variables: socio-economic status, including an asset score; quality of life (using the EQ-5D questionnaire [[41](#_ENREF_41), [42](#_ENREF_42)]); and social capital[[43](#_ENREF_43)].

***Patient and clinic factors***

***Patient factors:*** Data measured routinely included age, gender, baseline CD4 count (closest to ART initiation, up to 91 days before to 14 days after starting ART), baseline viral load (window as for CD4 count), WHO stage at baseline (within a month of starting ART), previous history of TB, previous ART use and ART regimen.

***Clinic factors:***  Scores were calculated for clinic infrastructure, staff leadership, motivation, burnout, monitoring and evaluation, integration, adherence interventions, and patient-provider relationship. Definitions for each clinic factor, as well as more explanation of each score, are shown in table 1. Data from the staff and patient questionnaires from the same clinic were summarised by calculating a mean score at the clinic level. Clinic factors were organised into four groups according to Lavis and colleagues [[18](#_ENREF_18)]: location of services, health providers, information and quality of services.

***Definition of outcomes:*** The three outcomes were: 1) Unsuppressed viral load at 24 months, defined as viral load ≥ 400 copies/ml on a single viral load measurement closest to the 24 month point (window 21-27 months), among those with a viral load measurement; 2) Time to loss to follow up: measured from the date of ART initiation to the earliest of death, loss to follow up, transfer out to a government programme or 31 December 2010. Date of loss to follow up was determined from deregistration forms or taken as 6 months after the last visit/lab test to the clinic if the patient was no longer active in the clinic. 3) Composite poor outcome at 24 months: viral load ≥ 400 copies/ml (as above), lost to follow up or death by 24 months among all patients started on treatment more than 24 months before 31 December 2010. Patients who were in care at 24 months but with no viral load result were excluded.

***Data analysis:*** The analysis to determine which clinic factors were associated with the outcomes was conducted in three stages (Appendix, Figure 1). Patients who died less than three months after ART initiation were excluded as deaths during this time were thought to be more closely related to WHO stage, CD4 count and body mass index than adherence to treatment[[44](#_ENREF_44)]. Stage 1 was based on constructing a model using variables measured at the patient-level. Stage 2 added variables measuring socio-economic status, captured on a sample of patients per clinic and therefore included as a clinic-level covariate. In stage 3, the association of clinic-level factors on the outcomes was assessed. For simplicity the model building for stages 1 and 2 was based on the outcome of unsuppressed viral load at 12 months.

For all models, random effects regression was used to account for clustering of patient outcomes within a clinic; random-effects logistic and Cox models were used for binary and time to event outcomes, respectively. P-values, assessing evidence for clustering, were reported. Each clinic-level variable was categorized either by using the lower and upper quartiles or an alternative categorization, if more established. The clinic-level variables were added to the model and tested for association with the outcome using the likelihood ratio test. Variables that remained associated with the outcome, based on P<0.1, were considered for the final model. As the number of clinics was relatively small, we limited the number of clinic-level variables that were included in the fully-adjusted model, by, where possible, only including one variable from each group of clinic-level variables [[18](#_ENREF_18)].

A sensitivity analysis was performed with adjustment for the additional patient variables on the subset of clinics which administered the more detailed questionnaire. For the sensitivity analysis, a full multivariable model adjusting for more than one clinic-factor was not developed due to the limited number of sites.

***Ethical considerations:*** The study was approved by the ethics committees of the London School of Hygiene and Tropical Medicine, United Kingdom and the University of the Witwatersrand, South Africa

 ***Sample size:*** Sample size calculations were based on formulae for cluster randomised trials[[45](#_ENREF_45)] for comparison of proportions. We assumed an average of 150 patients per clinic (cluster), type 1 error of 5%, and power of 80% and 90%. Coefficients of variation of 0.06 and 0.46, calculated from data collected routinely from the programme prior to study start, was assumed for unsuppressed viral load and loss to follow up, respectively. We conducted sample size calculations for a nominal clinic-level exposure assumed to be present in 50% of clinics. For unsuppressed viral load at 24 months, we would require a total of 36 clusters to determine an effect size of at least 1.25 (25% increase in unsuppressed viral load) with 90% power and an effect size of 1.20 with 80% power. For loss to follow up, a total of 36 clusters, could determine an effect size of at least 1.6 with 80% power and an effect size of 1.70 with 90% power.

**Results**

From 1 January 2006 to 31 December 2009, 10, 055 patients started ART at the 36 selected clinics and formed the cohort for analysis. Most patients were female (63%), ART-naïve (83%), and started stavudine-based regimens (88%); the median CD4 count at ART initiation was 114 cells/µl (interquartile range (IQR) 46 – 185). The median number of patients per clinic was 215 (range 69 – 1380) (Table 1).

By 24 months, 1241 (12.4%) had died, 2133 (21.2%) were lost to follow up, 442 (4.3%) had transferred out and 621 (6.2%) had not reached 24 months as they were enrolled in 2009 (figure 1). 5618 (55.9%) patients were still on treatment. Viral load results were available for 4,073 (74%), 676 (16.6%) had an unsuppressed viral load. The composite poor outcome of either unsuppressed viral load, loss to follow up, or death was determined in 6574 (78%; /8436) of patients at 24 months, 3440(52.3%) had a poor outcome.

At the clinic level, the mean proportion of patients with unsuppressed viral load at 24 months was 16% (range 8 – 33%, P for clustering 0.006). Deaths and loss to follow up were also highly variable across clinics ranging from 1.3 – 18.3/100 person-years (py) for deaths and 3.5 – 23.4/100py for loss to follow up (P for clustering 0.002). For the composite measure of poor outcome at 24 months the mean percentage across clinics was 53% (range 27 – 82%) (P for clustering <0.001). (Table 2)

Factors associated with increased odds of unsuppressed viral load at 24 months were younger age group (P trend 0.004), lower CD4 count at initiation (P trend 0.15), previous ART (OR 1.27, CI 0.98 – 1.63) and nevirapine NNRTI (OR 1.49, CI 1.21 – 1.84) as shown Table 3. In stage 2, the only patient-level variable measured at clinic level that was associated with unsuppressed viral load at 24 months, after adjustment for stage 1 variables, was socio-economic status, as measured by proportion of patients earning less than the national average [compared with <46%, 46-76% of patients below national average OR 1.40 (CI 0.79 – 2.46), >76% below national average, OR 1.96 (CI 1.06 – 3.64), P trend 0.02]. Results for these patient factors for poor outcome at 24 months and loss to follow up are shown in Table 3.

Clinic-level factors that remained associated with increased odds of unsuppressed viral load at 24 months, after adjusting for patient-level factors, were: clinics with lower doctor: patient ratio (compared with >2.6 doctors:500 patients: 0.7 – 2.6 doctors:500, adjusted OR 1.33, CI 0.91 – 1.93; <0.7: 500 patients adjusted OR 1.52, CI 1.04 – 2.21) (table 4). For the composite poor outcome, group practices compared with solo practitioners [adjusted OR 1.80, (CI 1.27 – 2.56)], lower cost of travel [compared to <24 ZAR: 12-24ZAR OR 0.99 (CI 0.67 -1.46) and <12 ZAR OR 1.45 (CI 0.94 – 2.25), P trend=0.1] and shorter clinic visit duration [compared to >90 minute mean visit duration: visit duration 50 -90 minutes, OR 1.47 (CI 1.03 – 2.11); visit duration <50 minutes, OR 2.11 (CI 1.34 – 3.33), P trend=0.003] were associated with increased odds of poor outcome.

Sites that used more adherence interventions in the clinic (>6 interventions vs <4 interventions: HR 0.24 [CI 0.09 – 0.75], P=0.001) were associated with reduced loss to follow up (table 4). Whereas, clinics with higher levels of staff experience (HR 2.37 of higher versus lower levels, [CI 1.39 – 4.07] were associated increased loss to follow up.

In a sensitivity analysis based on 19 clinics, controlling for measures of social capital and socio-economic status, clinic-level factors were examined individually for associations with unsuppressed viral load and time to loss to follow up. Lower monitoring and evaluation score was associated with increased odds of unsuppressed viral load (compared to score <19, score 12-19: OR 1.17 (95%CI 0.66 – 2.09) and >19: OR 2.14 (95% CI 1.05 – 4.34), P trend=0.05). In addition, lower nurse: patient ratio (nurse: patient ratios <1.14 nurse:500 patients OR 2.10 (95% CI 1.21 – 3.66) and no nurses OR 1.66 (1.21 – 3.66) compared to nurses >1.14:500 patients, P=0.05) and, as with the full analysis, lower doctor patient ratio (compared with >2.6 doctors:500 patients: 0.7 – 2.6 doctors:500, OR 1.39, CI 0.82 – 2.36; <0.7: 500 patients, OR 1.73, CI 1.02 – 2.92) were also associated with increased unsuppressed viral load.

For time to loss to follow up, the lower score for patient-provider relationship was associated with increased loss to follow up (compared to a score<36: score 36-48 HR 2.41, CI 0.66 – 8.77; and score>48, HR 13.35, CI 2.10 – 85.0, P= 0.04). Higher staff turnover (OR 2.38, CI 1.01 – 5.58) and higher staff burnout (compared to score <7.7: 7.7 -9.9, HR 2.47, CI 0.96 – 6.37; score>9.9, HR 3.82, CI 1.31 – 11.16, P trend =0.01) were also associated with increased loss to follow up.

**Discussion**

This observational study, using data from 36 clinics in four provinces in South Africa, found that after adjusting for patient factors, a lower doctor: patient ratio was associated with increased odds of unsuppressed viral load at 24 months in patients on ART, although this association was not found with the loss to follow up or composite poor outcome. . The importance of doctor: patient ratios has previously been shown in the cohort study conducted in 32 public sector clinics in KwaZulu Natal, South Africa, where the risk of default was higher in clinics with a lower doctor: patient ratio and with part-time doctors compared to full time doctors[[46](#_ENREF_46)]. No other studies have shown this association although many had attempted to measure staff: patient ratios but have not linked these to ART outcomes.

A higher number of interventions to improve adherence was associated with improved retention, lending support to the notion of “combination adherence promotion” (paraphrasing language used about HIV prevention). The main interventions used were: individual counselling (7 clinics), patient reminders (7 clinics), dedicated staff member to follow up patients (6 clinics), default tracers (5 clinics), pre-ART education sessions (4 clinics) and treatment supporters (4 clinics). Another study using aggregated data from different clinics[[47](#_ENREF_47)] in eight resource-limited countries, showed that having a combination of adherence counselling, structured treatment preparation and a community nurse reduced loss to follow up. Since our study was an evaluation under operational conditions we were not able to evaluate specific interventions to promote retention, however the study suggests that the more clinics do to promote retention, the better retention will be.

A higher mean score for patient-provider relationship, measured among a sample of patients at each clinic, was associated with reduced loss to follow up in the sensitivity analysis. This is supported by the better outcomes seen in clinics with patients who reported longer time at the clinic. by A qualitative interview study of the same programme emphasised the importance of a health provider having more time to form a relationship and discuss issues with the patient (Salome Charalambous - unpublished data).

The sensitivity analysis revealed additional clinic factors which on further analysis, we were able to determine, was likely due to the adjustment for additional socio-economic factors which indicate some residual effect of these factors on the association with outcomes in the main analysis.

Some of the findings, such as staff experience associated with poorer outcomes, were counterintuitive. Staff experience was also associated with male gender and older age of staff members and these may be confounding the association. In our study, longer travel time and higher cost of travel was not associated with poorer outcomes which differs from studies in Malawi, Nigeria and Tanzania [[14](#_ENREF_14), [48](#_ENREF_48), [49](#_ENREF_49)]. It could be that in South Africa, people have comparatively more disposable income and better road infrastructure making travelling easier and that, coupled with high stigma levels in the community [[26](#_ENREF_26), [50](#_ENREF_50)], may result in patients being more prepared to travel longer distances to attend clinics, where they feel care will be confidential.

The biggest strength of this study was the availability of the large number of clinics all using the same treatment guidelines, regimens, data collection tools and a single laboratory for CD4 and viral load monitoring. Another strength was the outcome of viral load, arguably the “gold standard” for monitoring ART. The use of additional outcomes of loss to follow up and the use of a composite outcome, combining retention in care and virological outcome, was a further strength. There are few other studies where clinic attributes were measured alongside ART outcomes [[51](#_ENREF_51), [52](#_ENREF_52)]. Our study also adopted an appropriate statistical analysis, taking into account the clustered design [[53](#_ENREF_53)]. Many studies looking at clinic factors often did not compare clinics directly or use an analysis taking into account the hierarchical nature of the data[[47](#_ENREF_47), [54](#_ENREF_54)]. This is however one of the first studies of its kind to try to adjust for patient factors that may explain differences in ART outcomes by clinic.

The use of the routine data led to an analytical limitation as it was not possible to control for individual-level factors such as disclosure of HIV status, use of traditional medicines, religious beliefs and socio-economic status that may determine ART outcomes. To quantify these variables, data were collected from a sample of patients at each clinic and was used in the multivariable model to characterize the clinic populations. However, there may be incomplete control for confounding since data on these factors were not available for every patient included in the main analysis. In addition, the usual problems with routine data were encountered such as missing data, however we did account for patients with missing viral load in the composite outcome analysis. We also feel that for some clinic factors, such as quality of counselling or quality of clinical care, the measurement may have been superficial and would ideally have required a more detailed assessment.

The clinics included a range of provinces and social contexts, and were made up of small and large practices and so we believe the findings should be relevant in a range of settings, including public facilities. Staff in our study were generally highly motivated and had low burn out. This may differ from public sector facilities: previous studies have shown relatively high motivation [[37](#_ENREF_37), [55](#_ENREF_55)] [[56](#_ENREF_56)], but high levels of burnout among staff at public facilities[[37](#_ENREF_37)]. We believe that our patients are not too dissimilar to public sector patients as only those who could not afford treatment themselves (earning less than 5000ZAR per month) could be included in the programme, which provided free medication, and the issues examined in this study (of leadership, staffing levels, burn out, staff motivation) would be relevant to most health care delivery clinics.

The findings of this study emphasize the importance of staff: patient ratios and the patient-provider relationship. In the context of scarce human resources, the study findings suggest that antiretroviral delivery is unlikely to become easier for countries to implement. Task-shifting has begun and will need to continue to be implemented to allow for sufficient time for counselling and patient interaction in countries with limited medically-trained personnel. This study supports the implementation of “combination adherence promotion“, however further research is needed to identify which activities undertaken by clinics are most effective in promoting retention. As the need to sustain more and more people on ART increases, the need to understand how to optimize treatment outcomes and maintain quality of care will become ever more important.

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**Figure 1. Flow diagram of patient cohort and outcomes**

10 055 adult patients from 36 clinics included in the study

1from sites where patient cohort was moved to another programme prior to end of the study or due to transfers to other programmes due to patient request.

2patients on treatment for <24 months or from sites

**24 months**

1241 died (556 in first 3 months)

6212 No opportunity for 24 months follow up

4421 transferred to other programme

**4073 Viral load results**

On treatment: 5618; 36 clinics

2133 loss to follow up

Table 1. Summary table of clinic variables that were examined for association with patient outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Clinic factor | Data collection tool | Measurement | Percentage (n/36)1 or Mean (range)  |
| LOCATION OF SERVICES |
| General characteristics of clinic | type of clinic | CQ | NGO, group practice solo practitioner | 8% (3/36), 17% (6/36), 75% (27/36) |
|  | HIV dedicated clinic | CQ | reported as dedicated to HIV patients only | 19% (7/36) |
|  | provision of child services | CQ | reported as providing services to children | 48% (15/36) |
| Infrastructure | clinic infrastructure | CA | total score of facility assessment2 | 41 (23 – 49) |
| Geographic location | location of clinic | CQ | city, town or rural | 18 (50%), 15 (42%), 3(8%) |
|  | duration of travel to clinic (minutes) | PQ | median duration of travel per clinic as reported by patients  | 15 (15 – 60) |
|  | cost of travel (ZAR) | PQ | median cost of travel per clinic as reported by patients | 15.3 (0-50) |
| HEALTH PROVIDERS |
| Staffing structure | availability of lay counsellors | CQ | lay counsellor used | 61% (22/36) |
|  | availability of clinic manager | CQ | clinic manager identified | 25% (9/36) |
| Workload | doctors: 500 patients3 | CQ | calculation of FTE dedicated to Aurum patients | 1.64 (0 – 5.24) |
|  | nurses: 500 patients3 | CQ | calculation of FTE dedicated to Aurum patients | 0.68 (0 – 4.95) |
|  | staff: 500 patients3 | CQ | calculation of FTE dedicated to Aurum patients | 5.55 (0.64 – 18.59) |
|  | patients seen per day | SQ | mean patients seen on last most busy working day in the past week | 16 (3-53) |
| Staff experience | staff experience | SQ | proportion of staff with >3years experience of patients on ART | 88% (50 – 100) |
| Staff management | staff leadership4assessment | SQ | mean leadership assessment by staff member5 | 13.8 (9- 17) |
| Staff attitude | motivation score | SQ | motivation score6 | 43.2 (34.7 – 50) |
|  | burnout score | SQ | burnout score7 | 8.7 (6 -12.5) |
|  | staff turnover  | CQ | staff change in the past year | 64% (23/36) |
| Staff training | training in last 12 months | SQ | mean number of trainings per staff member | 2.7 (0 – 8) |
| INFORMATION |
| Monitoring and evaluation | combined M&E score | CA | score for record keeping and electronic register8 | 14.5 (4-21) |
| QUALITY OF SERVICES |
| Integration | number of available of services | CQ | HCT, PMTCT, curative care, antenatal care, obstetric deliveries, chronic disease care, on-site pharmacy, TB sputum microscopy, TB sputum culture and x-ray facilities. | 6 (2-9) |
|  | assistance with disability grants | CQ | availability of assistance with disability grants | 78% (n/36) |
|  | referral to other providers | CQ | referral to providers | 3 (0 - 11) |
| Flexibility of hours | flexibility of hours | CQ | composite score for flexibility9 | 3 (0-4) |
| Availability of guidelines | number of guidelines available | CA | number of guidelines | 8 (2-12) |
| Adherence support | active adherence interventions | CQ | adherence interventions score10 | 5 (2 - 8) |
|  | quality of counselling | PQ | proportion of patients satisfied by counselling length | 72.7 (50 -95) |
| Patient tracing | patient tracing for loss to follow up | CQ | presence of either default tracer or NGO or home based care workers to trace patients | 50% (18/36) |
| Patient-provider relationship | patient-provider relationship | PQ | mean patient score of patient-provider relationship11 | 52.2 (45 -58) |
| Clinic duration | duration of clinic visit | PQ | median duration of quarterly visits as reported by patients | 60 (15 – 300) |

 CQ = Clinic questionnaire, CA = Clinic assessment, PQ = Patient questionnaire , SQ = staff questionnaire, FTE = full-time equivalent; NGO = non-governmental organisation

HCT = HIV Counselling and Testing, PMTCT = Prevention of Mother to Child Transmission Treatment

1 Mean and range for continuous variables and proportion (%) for categorical variables

2Scores for waiting area and reception (13); observations room (8); consultations (5); counselling rooms (3); toilet facilities used by patients (11); HIV counselling and testing (4); educational materials (3); dispensing room(4), maximum score = 51

3 Doctor, nurse and staff load only available on 35 clinics

4 Leadership assessment available on 34 clinics

5 Questions regarding assessment of leader, including availability, ability to motivate staff, charisma and caring for staff, maximum score = 16

6 Likert responses (0-5) from Kenyan validated questionnaire (10 questions), maximum score=50, questions include overall motivation levels, pride in work and willingness to work7 Burnout Inventory (6 questions), maximum score=30, questions regarding empathy and depersonalization which were thought to affect patient interactions

8 Maximum score=6, questions regarding electronic registers, security of data, facilities for data capture

9 Availability of clinic/doctor after hours, weekends, afternoons, maximum score=4

10 Use of various adherence support interventions reported, such as individual counselling, treatment supporters, home visits, electronic reminders, support groups, tracing of patients, education sessions, pill counts, directly observed therapy or dedicated staff for follow up, maximum score=10

11 Quality of patient-provider relationship questionnaire; mean of all patients in a clinic, maximum score=60, questions such as compassion, understanding, friendliness, attitude of staff

Table 2. Outcomes summarised, overall and at the clinic-level (mean, range) and p value for between-clinic variation

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | OVERALL SUMMARY (ignoring cluster) | CLINIC-LEVEL SUMMARY (n=36) |
|  | **Patients with results** | **Outcome (% or rate per 100 py)** | **Mean**  |  | **Range**  | **Measure of clustering4****(P value)** |
| Unsuppressed viral1 load at 24 months |  |  4073 16.6%  | 16% |  | 8% - 33% | 0.006 |
| Poor outcome2 at 24 months |  |  6574 47%  | 53% |  | 27% - 82% | <0.001 |
| Death rate | 35346py | 3.88/100py | 3.94 |  | 1.29–18.28 | 0.002 |
| Loss to follow-up3 rate | 35346py | 9.13/100py | 9.91 |  | 3.48 – 3.41 | 0.002 |

1 Viral load ≥ 400 copies/ml

2 Viral load ≥400copies/ml or loss to follow up or death; patients who had died within 3 months of starting ART or who were in care at the time point of the outcome but with no viral load result were excluded.

3 Date of loss to follow up was determined from deregistration forms or defined as 6 months after the last visit/laboratory test to the clinic if the patient was no longer active in the clinic. Patients who died were not defined as lost to follow up.

4 Test of rho=0 for binary outcomes (logistic regression) or alpha for time to event (Poisson regression).

Py person-years

**Table 3. Multivariable model (“Stage 2 model”) including patient variables measured at clinic-level for unsuppressed viral load and poor outcome1at 24 months and time to loss to follow up**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Unsuppressed viral load at 24 months | Poor outcome at 24 months | Loss to follow up |
|  | N=4073 | **Multivariable** (N=3403)2 |  | **Multivariable3** (N = 5367)4 |  |  | **Multivariable** (N=8303)5 |
|  | **n/N (%)** | **OR (95% CI)** |  **n/N (%)** | **OR (95% CI)** | **N/ pys** | **Rate per 100 pys** | **HR (95% CI)** |
| PATIENT VARIABLES MEASURED AT PATIENT-LEVEL |
| Gender Male  Female | 312/1891(17)588/2292(17) | 1 *P=0.1*0.83 (0.66 – 1.03) | 1379/2492(55)2061/4082(50) | 1 *P=0.003*0.81 (0.70 – 0.92) | 1339/136171888/21728 | 9.838.68 | 1 *P<0.001*0.84 (0.76 – 0.92) |
| Age (years)  <30 30 - 39 40 - 49 ≥ 50 | 218/1078(20)442/2444(18)189/1297(15)50/464(11) | 1 PT*=0.004*0.85 (0.67 – 1.07)0.80 (0.61 – 1.06)0.52 (0.34 – 0.79) |  766/1367(56)1535/3006(51) 819/1590(52) 320/611(52) | 1 *PT=0.04*0.86 (0.74 – 1.00)0.82 (0.69 – 0.98)0.83 (0.67 – 1.04) | 740/75211433/16103770/8569284/3126 | 9.848.908.969.09 | 1 *PT=0.69*0.90 (0.81– 1.00)0.96 (0.85 – 1.08)1.03 (0.89 – 1.21) |
| WHO stage at ART initiation  1  2 3 4 | 100/655(15)125/971(17)251/2018(17)200/1180(17) | 1 *PT=0.95*1.02 (0.73 – 1.42)1.07 (0.77 – 1.46)1.07 (0.77 – 1.49) |  528/1013(52) 572/1148(50)1259/2397(53)1081/2016(54) | 1 *PT=0.02*1.00 (0.80 – 1.23)1.00 (0.82 – 1.22)1.22 (0.99 – 1.51) | 516/5220571/59061148/12499992/11721 | 9.889.679.198.46 | 1 *PT<0.001*0.89 (0.76 - 1.03)0.82 (0.72 – 0.95)0.75 (0.65 – 0.87) |
| Baseline CD4 count  >350 201 – 350 51-200 ≤ 50  | 46/298 (15)100/634 (16)350/2185(16)159/856 (19) | 1 *PT=0.15*1.00 (0.64 – 1.55)1.10 (0.73 – 1.66)1.27 (0.81 – 1.98) | 159/389(41) 411/879(47)1734/3433(51) 987/1650(60) | 1 PT<0.0011.27 (0.94 – 1.71)1.30 (0.98 – 1.71)1.78 (1.33 – 2.39) | 152/1949395/45291670/18029865/9437 | 7.808.729.269.17 | 1 *PT=0.02*1.09 (0.86 – 1.37)0.89 (0.72 – 1.11)0.88 (0.70 – 1.11) |
| Previous ART No Yes  | 137/783(18)447/2749(16) | 1 *P=0.07*1.27 (0.98 – 1.63) | 2438/4551(54) 418/1020(41) | 1 *P=0.004*0.77 (0.66 – 0.91) | 2322/24121351/5348 | 9.636.56 | 1 *P<0.001*0.66 (0.58 – 0.75) |
| NNRTI in initial regimen  efavirenz  nevirapine  | 294/2111(14)362/1502 (19) | 1 *P<0.001*1.49 (1.21 – 1.84) | 1925/3611(53)1419/2793(51) | 1 *P=0.47*0.96 (0.84 – 1.09) | 1870/196681268/14768 | 9.518.59 | 1 *P=0.02*1.13 (1.02 – 1.25) |
| PATIENT VARIABLES MEASURED AT CLINIC-LEVEL |
| %Income < national average (ZAR 2100) <46% 46 – 76% >76% | 32/239 (14)540/2738 (16)104/556 (17) | 1 *PT=0.02*1.40 (0.79 – 2.46)1.96 (1.06 – 3.64) | 201/515 (39)2529/4989 (51)404/1070 (38) | 1 *PT=0.35*0.74 (0.41 – 1.33)1.08 (0.56 – 2.06) | 391/29842318/27035518/5326 | 13.108.579.72 | 1 *PT=0.02*1.00 (0.34 – 2.97)2.51 (0.77 – 8.14) |

NNRTI=non-nucleoside reverse transcriptase inhibitor; *PT* = P value for linear trend; ZAR=South African rands; OR=odds ratio; HR=hazard ratio; CI=confidence interval; ART=antiretroviral therapy; WHO=World Health Organization; pyrs person-years

1Viral load >400copies/ml or loss to follow up or death (death before 3 months after starting ART excluded)

2Rho= 0.017, Likelihood ratio test for Rho=0, P=0.02

3Adjusted for gender, age group, WHO stage at ART initiation, CD4 count at ART initiation, previous ART, NNRTI regimen and % income below national average

4Rho= 0.06, Likelihood ratio test for Rho=0, P<0.001

5 Theta=0.77, Likelihood ratio test for theta=0, P<0.001

**Table 4. Multivariable model showing clinic-level factors associated with unsuppressed viral load at 24 months, time to loss to follow up, and composite poor outcome at 24 months controlled for patient factors, measured at patient and clinic level**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| Clinic characteristic (unit, total score) |  | Details | Multivariable |
| UNSUPPRESSED VIRAL LOAD | **No of clinics** |  | **(N=3365, 35 clinics)2,3** |
|  |  | **Categorised variables** | **OR (95% CI)** |
| Doctor load*(doctors: 500 patients)* | 8189 | >2.60.7 – 2.6<0.7  | 1 PT=0.041.33 (0.91 – 1.93)1.52 (1.04 – 2.21) |
|  |  |  |  |
| Flexibility of hours(*max score 4)* | 1422 | Low flexibility (1 or 2)High flexibility (3 or 4)  | 1 P=0.061.26 (1.00– 1.59) |
|  |  |  |  |
| Patient-provider relationship4(*max score 60*) | 10197 | <3636 – 48>48 | 1 P=0.111.07 (0.82 – 1.41)1.37 (1.02 – 1.85) |
| COMPOSITE POOR OUTCOME5 (N=5307, 35 clinics)7 |
|  |  |  | **Multivariable6** |
|  |  | **Categorical variables** | **OR (95% CI)** |
| Type of clinic *(cl)*  | 2763 | Solo practitionerGroup practice Non-governmental clinic  | 1 P=0.0081.80 (1.27 – 2.56)0.99 (0.60 – 1.63) |
|  |  |  |  |
| Mean cost of travel to clinic*(Mean cost)* | 8217 | >24 ZAR12 – 24 ZAR<12 ZAR | 1 PT=0.10.99 (0.68 – 1.46) 1.45 (0.94 – 2.25)  |
|  |  |  |  |
| Mean duration of clinic visit*(Mean time)* | 9198 | >90 minutes50 – 90 minutes<50 minutes  | 1 PT=0.0031.47 (1.03 – 2.11)2.12 (1.34 – 3.34) |
| LOSS TO FOLLOW UP |  |  | (N=7504, 31 clinics)89 |
|  |  |  | **HR (95% CI)** |
| Adherence interventions(*max score 10*) | 9225 | <4 interventions4 – 6 interventions >6 interventions | 1 P=0.0011.23 (0.67 – 2.26)0.24 (0.09 – 0.60) |
|  |  |  |  |
| % Staff >3 years’ experience *(% staff with >3 years ART experience)* | 1521 | <62%>62% | 1 P<0.0012.37 (1.39 – 4.07) |

OR=odds ratio, HR=Hazard ratio, CI=confidence interval, PT=P value for trend

1 Specified at which level information is collected: clinic (cl), staff (st), patient (pt)

2Adjusted for gender, age group, WHO stage at ART initiation, CD4 count at ART initiation, previous ART, NNRTI regimen, % income over GDP, doctor load, flexibility of hours and quality of care

3 Rho< 0.0001, Likelihood ratio test for Rho=0, P=0.493

4 Quality of care: 12 questions, likert score (1-5), “Don’t know” and missing coded as 3:

5Composite poor outcome: death after 3 months, unsuppressed viral load or loss to follow up

6 Adjusted for gender, age group, WHO stage at ART initiation, CD4 count at ART initiation, previous ART, NNRTI regimen, % income over GDP, doctor load (linear), type of clinic, staff experience, cost of travel (linear) and duration of clinic visits (linear)

7 Rho= 0.03, Likelihood ratio test for Rho=0, P<0.001

8 Adjusted for gender, age group, WHO stage at ART initiation, CD4 count at ART initiation, previous ART, NNRTI regimen, % income over GDP, cost of travel (linear), staff experience, cost of travel (linear) and adherence interventions

9 Theta=0.52, Likelihood ratio test for theta=0, P<0.001

10 available on 9140 patients, 31 of 36 clinics