Published in final edited form as:

AIDS. 2011 October 23; 25(16): . doi:10.1097/QAD.0b013e32834b6480.

Outcomes of stable HIV-positive patients down-referred from doctor-managed ART clinics to nurse-managed primary health clinics for monitoring and treatment

Alana Brennan^{1,2,3,†}, Lawrence Long^{1,3}, Mhairi Maskew^{3,4}, Ian Sanne^{4,5}, Imogen Jaffray⁵, Patrick MacPhail^{4,5}, and Matthew P. Fox^{1,2,3,6}

¹Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

²Center for Global Health and Development, Boston University, Boston, USA

³Faculty of Health Sciences, University of the Witwatersrand, South Africa

⁴Clinical HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

⁵Right to Care, Johannesburg, South Africa

⁶Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

Abstract

Objective—Compare clinical, immunologic and virologic outcomes amongst stable HIV-positive patients down-referred (DR) to nurse-managed primary health care clinic (PHC) for treatment maintenance to those who remained at the doctor-managed treatment-initiation site (TI).

Design—We conducted a matched cohort analysis amongst stable HIV patients at the Themba Lethu Clinic, in Johannesburg, South Africa. Eligible patients met the criteria for down-referral (undetectable viral load <10-months, ART >11-months, CD4 >200cells/mm³, stable weight and no opportunistic infections) regardless of whether they were down-referred to a PHC for treatment maintenance between February 2008-January 2009. Patients were matched 1:3 (DR:TI) using propensity scores.

Methods—We calculated rates and hazard ratios for the effect of down-referral on loss to follow-up (LTFU) and mortality and the relative risk of down-referral on viral rebound by 12-months of follow-up.

Results—693 DR patients were matched to 2079 TI patients. Two (0.3%) DR and 32 (1.5%) TI patients died, 10 (1.4%) DR and 87 (4.2%) TI were lost, while 22 (3.3%) DR and 100 (5.6%) TI experience viral rebound by 12-months of follow-up. After adjustment, patients down-referred were less likely to die (HR 0.2; 95% CI: 0.04-0.8), become LTFU (HR 0.3; 95% CI: 0.2-0.6) or experience viral rebound (RR 0.6; 95% CI 0.4-0.9) than TI patients during follow-up.

Conclusions—The utilization of nurse-managed PHCs for treatment maintenance of stable patients could decrease the burden on specialized doctor-managed ART clinics. Patient outcomes

[†]**Corresponding Author Details:** Center for Global Health and Development Boston University Crosstown Center, 3rd Floor, 801 Massachusetts Ave Boston, MA 02118 Phone: 617-414-1260, abrennan@bu.edu.

Potential Conflicts of Interest: Right to Care provided some of the funding for the current research and also supports the provision of treatment for the patients in the study.

for DR patients at PHCs appear equal, if not better, than those achieved at ART clinics amongst stable patients.

Keywords

antiretroviral therapy; task-shifting; nurse-managed vs. doctor-managed care; mortality; loss to follow-up; resource-limited setting; scaling-up

INTRODUCTION

Roughly five million people living with HIV in low- and middle-income countries are currently receiving antiretroviral therapy (ART), up from about 400,000 in 2003[1], representing over a 12-fold increase over six years. Despite these gains, only one-third of those in need are receiving ART in resource-limited settings[1]. The increase in the number of eligible patients accessing care coupled WHO recommendations to treat patients at higher CD4 counts[2] has put pressure on health systems and pushed governments to seek new models of treatment delivery.

Scaling-up ART requires large numbers of well-trained health-care workers[3]. Several needs assessments have shown limited capacity to scale-up services using doctors[K Gilbert et al., unpublished data, 2005; B Damascene et al., unpublished data, 2005; 4]. Models of care adapted from industrialized countries typically have a large doctor-patient ratio coupled with increasing demand, a shortage of trained medical staff and limited finances. To address these concerns, decentralizing care to smaller health facilities along with ‘task-shifting’ care from doctors to clinical officers, nurses[5-9] and community health workers[7,8,10] have been proposed.

Although ‘task-shifting’ is a potential solution to expanding pressures on the health care system[7,11-13], the evidence for non-physician provided HIV care in Africa is limited[14-21]. The majority of the evidence-base comes from studies conducted in resource-rich settings comparing primary care provided either by doctors, physician assistants or nurse practitioners. These studies helped provide evidence that non-physicians can manage chronic diseases as effectively as doctors[22,23], though none assessed HIV care. A recent systematic review demonstrated that ‘task-shifting’ in sub-Saharan Africa helped increase access to ART and that lower level clinic staff could provide high quality care compared to clinicians[24]. Several studies have also shown that retention and clinical outcomes were better in facilities with fewer patients, supporting decentralization of HIV treatment[25,26], but ‘down-referral’ will require careful planning and monitoring[21].

In response to these issues, South Africa’s National Department of Health began decentralizing care of stable patients initiated and managed by doctors at higher levels of the health care system, to smaller health facilities employing nurse-managed care[9]. In 2007, the Themba Lethu HIV Clinic (TLC) in Johannesburg, South Africa implemented a ‘down-referral’ system to transfer stable patients from the doctor-managed clinic where they initiated care (TLC) to nurse-managed local primary health clinics (PHC) for continued monitoring and treatment. Nearly 2,000 patients have been down-referred from TLC, yet treatment outcomes amongst these patients have yet to be evaluated. This study compares one-year treatment outcomes amongst individuals down-referred for treatment maintenance at a nurse-managed PHC to patient’s eligible for down-referral who remained at the doctor-managed treatment-initiation site in Johannesburg, South Africa.

METHODS

Cohort description

TLC is a government HIV treatment site, which has enrolled over 28,500 patients into care, over 18,500 of which have initiated ART since its inception in April 2004. The clinic sees 400-500 patients a day, has eight doctors and twelve nurses. In February 2007 TLC began piloting down-referral by transferring stable patients to PHCs for monitoring and treatment. Currently there are two down-referral sites, this analysis focuses on the first site established, Crosby Clinic, a PHC in close proximity to TLC.

Crosby clinic sees 80-90 patients a day and is staffed by two nurses. A section of Crosby Clinic was refurbished and equipped with a down-referral wing and pharmacy operated independent of the clinic. The site remains integrated with TLC through an electronic patient management system, TherapyEdge-HIV™. TherapyEdge-HIV™ transfers patient records between TLC and down-referral sites whenever a patient is down-referred or up-referred (transferred back to the treatment-initiation site). The system alerts providers when patients are eligible for down-referral or requires up-referral.

Crosby Clinic nurses are trained primary health care nurses qualified to diagnose, treat and prescribe drugs for specific conditions, including HIV. They receive an additional six-week down-referral training conducted at TLC covering HIV disease, treatment, monitoring and adherence. In the six-week training nurses are supervised daily by a senior nurse, doctors and the down-referral coordinator. Supervision then continues telephonically by nurses or clinicians at TLC. If nurses are not able to handle a patient's condition they would be up-referred to TLC and treated by a clinician. Additionally, TherapyEdge-HIV™ has an electronic treatment algorithm to guide nurses in patient care.

Data was approved for analysis by the Human Research Ethics Committee of the University of the Witwatersrand. Approval for analysis of de-identified data was granted by Boston University's Institutional Review Board of.

Down-referral process

All patients included in this analysis initiated treatment at TLC (referred to hereafter as the treatment-initiation site). Patients who are eligible for and accept down-referral are moved to a local PHC (referred to hereafter as the down-referral site). While 'down-referral' and 'task-shifting' are not always synonymous, in South Africa they typically are as lower-level facilities tend to have lower cadres of staff. This program used both down-referral to a PHC clinic and task-shifting by having patients managed by nurses rather than clinicians.

To be eligible for down-referral a patient must have been on ART for at least eleven months, giving clinicians two sets of labs to evaluate the patient (4-months and 10-months on ART). Patients must have no opportunistic infections, a CD4 count >200 cells/mm³, a stable weight ($<5\%$ loss between last three visits) and be virally suppressed (two consecutive viral loads <400 copies/ml). Patients meeting eligibility criteria and whom clinicians feel are good candidates for down-referral are given the option to transfer. Over 65% of patients eligible for down-referral were not transferred to the PHC. For some this represents refusal of down-referral, while for most it represents not being offered down-referral. Our data cannot distinguish between the two reasons.

Patients accepting down-referral are dispensed two months of ARVs and scheduled to present to the down-referral site two months later. Down-referred patients are scheduled for ARV pickups every two months, same as at the treatment-initiation site. Patients at the treatment-initiation site have a doctor consultation every six months; while down-referred

patients have a nurse take vitals at every visit. Care at both sites follows South African National Treatment Guidelines, which during the study period called for treatment with stavudine or zidovudine with lamivudine and either efavirenz or nevirapine. CD4 and viral load tests were done approximately six-monthly[9,27].

Patients can also be up-referred to the treatment-initiation site. The majority of up-referrals (44.5%) occurred for defaulting (missing a visit by 7 days). Defaulters are automatically up-referred by TherapyEdge-HIV™ and can only return to the down-referral site when a clinician recommends it. Patients who become loss to follow-up at the down-referral site are up-referred and counselors attempt to contact them by phone or home visit to return them to care. Other reasons for up-referral include ARV toxicities (24.5%), pregnancy (11.0%), detectable viral load (4.2%) and opportunistic infections (4.2%).

All patients at TLC receive adherence counseling before treatment initiation. If a down-referred patient has a detectable viral load nurses counsel them and perform a second viral load. If detectable, patients are up-referred and again receive formal adherence counseling.

Study population

Patients eligible for this study were ART-naïve at treatment initiation at TLC, 18 years old and initiated onto a standard first-line ART regimen between April 2004 and September 2008. We excluded pregnant patients, those on second-line therapy and patients not eligible for down-referral (Figure 1). We removed all patients missing data necessary for matching.

Since down-referral was not randomly assigned, we used propensity score matching to create similar populations of down-referred and not down-referred but eligible patients[28-30]. To create propensity scores we predicted risk of down-referral using logistic regression. Predictor variables included gender, age, months on ART, ARV regimen, body mass index (BMI), haemoglobin and CD4 count at down-referral eligibility(Appendix 1). Propensity scores were used to individually match down-referred patients to three patients eligible for down-referral but remaining at the treatment-initiation site[31].

Study variables

We compared death, loss to follow-up, mean CD4 change from down-referral eligibility and viral load rebound by 12-months of follow-up by down-referral status. Down-referral was defined as completion of the down-referral visit at TLC between February 2008 and January 2009. Deaths are identified by family or hospital report, active tracing and/or linkage with the South African National Vital Registration Infrastructure Initiative[32-34]. Loss to follow-up was defined as at least 3-months late for the last scheduled visit. Viral load rebound was defined as having a detectable viral load (>400 copies/mL) at 12-months after down-referral eligibility.

Time zero was defined as down-referral eligibility for all patients regardless of whether they were actually down-referred. For analyses of death and loss to follow-up, person-time accrued from down-referral eligibility until the earliest of: 1) death; 2) loss to follow-up; 3) transfer; 4) completion of 12-months of follow-up; or 5) December 31st 2009.

Statistical analyses

We calculated rates of loss to follow-up and mortality over 12-months of follow-up stratified by down-referral status. For both outcomes we estimated hazard ratios by down-referral status using proportional hazards regression. To estimate the relative risk of viral load rebound by down-referral status we used log-linear regression. All models were adjusted for national identification number, gender, age, ART regimen and CD4 count at down-referral

eligibility. Covariates that could be plausible confounders that altered the point estimate by 10% or more were also included. We assessed modification of the effect of down-referral on outcomes by stratifying effect measures by plausible modifiers.

As we may have had unmeasured confounding in our population we conducted a multidimensional sensitivity analysis[35], by making assumptions about the strength of the effect of an unmeasured confounder on mortality and its prevalence in both down-referred and not down-referred patients. As we were interested in confounders that would overestimate the down-referral effect, we considered a confounder that would increase mortality and was more prevalent in patients remaining at the treatment-initiation site. We then back-calculated the relative risk we would have observed had we collected data on and adjusted for the purported confounder(Appendix 2)[36].

RESULTS

1,579 patients were down-referred to the PHC and 3,421 were eligible but remained at the treatment-initiation site. Of those down-referred 774 were not eligible as they were either down-referred outside the study period, pregnant or on a second-line regimen (Figure 1). We excluded 95 patients missing data necessary for matching and 17 patients down-referred without meeting down-referral eligibility criteria, leaving 693 down-referred patients. Of the 3,421 eligible patients remaining at the treatment-initiation site we excluded 453 patients missing data necessary for matching, leaving 2,968 patients. The 548 patients excluded for missing data were similar to those included in regards to demographic and clinical characteristics at down-referral eligibility.

Predictors of down-referral

Less advanced disease at down-referral eligibility was associated with down-referral. A CD4 count of ≥ 300 cells/mm³ was associated with greater odds of down-referral versus 200-299 cells/mm³. Having a BMI ≥ 17.5 vs. <17.5 kg/m² (OR 1.7; 95%CI: 0.8-3.4), a haemoglobin ≥ 10.0 vs. <10.0 ug/dL (OR 2.0; 95%CI: 1.1-3.8) and taking stavudine vs. zidovudine (OR 1.2; 95%CI: 1.0-1.5) were also predictive of down-referral(Table 1).

Matched cohort

The 2,772 patients included in the analysis had a median age of 35.3 years (IQR: 30.8-41.6), a median CD4 count of 389 cells/mm³ (IQR: 311-507), were predominately female (65.7%), on ART for a median of 30 months (IQR: 22.3-42.0) and on stavudine-lamivudine-efavirenz (64.8%) at down-referral eligibility(Table 2). Propensity score matching of the 693 down-referred patients to 2,079 patients remaining at the treatment-initiation site created similar populations in terms of baseline characteristics predictive of poor prognosis as well as demographic and clinical characteristics at down-referral eligibility(Table 2).

Mortality and Loss to follow-up

Two (0.3%) down-referred patients and 32 (1.5%) not down-referred died, while 10 (1.4%) down-referred and 87 (4.2%) not down-referred were lost during 12-months of follow-up(Table 2). Median time to death and loss from down-referral eligibility was 5.0 months (IQR: 2.1-8.4) and 6.9 months (IQR: 4.9-9.2), respectively. The mortality rate was lower among down-referred patients (0.3/100 pys) than among those remaining at the treatment-initiation site (1.6/100 pys)(adjusted HR: 0.2; 95%CI: 0.04-0.8). After adjustment, down-referred patients were still less likely to become lost than those remaining at the treatment-initiation site (HR 0.3; 95%CI: 0.2-0.7)(Table 3). When stratifying by potential modifiers we found the association of down-referral with a reduction in loss to follow-up was stronger amongst patients with a CD4 count ≥ 350 cells/mm³ (IRR 0.1; 95%CI: 0.05-0.3) than among

patients with a CD4 count of 200-349 cells/mm³ (IRR 0.5; 95%CI 0.2-1.3) and stronger among females (IRR 0.2; 95%CI: 0.1-0.6) than males (IRR 0.5; 95%CI: 0.2-1.3).

Sensitivity Analysis

A sensitivity analysis for unmeasured confounding shows that in order for adjustment for an unmeasured confounder to bring our results close to null, it would have to be rare amongst down-referred patients (1.0%) and common among treatment-initiation site patients (45%) and be a very strong predictor of mortality (RR = 12)(Appendix 2), an unlikely scenario.

CD4 response and viral rebound

The majority (95%) of down-referred patients and 81% of patients not down-referred had a 12-month CD4 count and viral load available. Patients missing data were similar in regards to age, CD4 count at down-referral eligibility, time on ART, gender and current regimen to those included. The median increase in CD4 count over 12-months for those down-referred was 55 cells/mm³ (IQR: -24-127) and 59 cells/mm³ (IQR: -12-146) for patients not down-referred.

Twenty-two (3.3%) patients down-referred and 100 (5.6%) not down-referred experienced viral load rebound (>400 copies/ml) by 12-months since down-referral eligibility. Adjusted analyses showed down-referred patients had a reduced risk of viral rebound (RR 0.6; 95%CI: 0.4-0.9) compared to treatment-initiation site patients (Table 3). We observed little modification of the down-referral association with viral load rebound.

DISCUSSION

Decentralization of monitoring and treatment of HIV-positive ART patients and 'task-shifting' from doctor-managed to nurse-managed care have proven successful in supporting rapid scale-up of ART in resource-limited settings[14-21]. Providing ART at PHCs encourages retention in and increases access to care[1,2,5,6]. We found a large proportion (40%) of patients initiating ART between April 2004 and January 2009 were eligible for down-referral. Because patients had been on ART for a median of 30 months (IQR 22-42), were clinically stable and virally suppressed prior to eligibility the outcomes we observed were very good, with very little mortality. However, we still found that down-referred patients had similar, if not better, clinical and virologic outcomes than those remaining at the treatment-initiation site. Down-referred patients had lower mortality (HR 0.2; 95%CI: 0.04-0.8) and were less likely to become lost (HR 0.3; 95%CI: 0.2-0.6) or experience viral load rebound (RR 0.6; 95%CI: 0.4-0.9) than those remaining at the treatment-initiation site. While we cannot say that these beneficial outcomes were caused by down-referral, our matching strategy and sensitivity analysis suggest that at a minimum, down-referred patients managed by nurses will do no worse than those managed by doctors. These findings are consistent with previous reports from sub-Saharan Africa showing ART outcomes were comparable for care provided by nurses and doctors[6,14]

In April 2010 the South African National Department of Health shifted focus from the 'down-referral' model of care to a nurse-initiation and management ('NIM-ART') model to expand ART access[9]. NIM-ART is a more comprehensive version of the current 'down-referral' model, using a combination of task-shifting (nurses initiating and prescribing repeat ARVs) and integration of comprehensive HIV care into PHC services[9]. NIM-ART is currently being evaluated by the STRETCH trial[37]. Qualitative findings suggest NIM-ART is feasible and acceptable in the public sector and that well-equipped nurses in PHC settings can provide HIV care[38]. Our findings support the move to towards nurse-centered care.

Two potential reasons why our down-referred patients had slightly better outcomes than those not down-referred may be: (1) more frequent medical screenings, allowing opportunities to diagnose new infections or drug toxicities earlier and (2) increased patient satisfaction with care and treatment received at the down-referral site. Over 300 down-referred patients at Crosby Clinic were surveyed about the time, cost, ease and quality of care at the site. Results showed that >90% completed their visit within one hour and believed the nurses attended to their medical needs and could sustain their care for years to come. Since the patient satisfaction survey was not administered at TLC we do not have a comparison group. However, a recent analysis of patient flow at TLC showed patients spent (including waiting time) a median of 2.5 hours (IQR: 1.2-4.2) per medical visit and 1.9 hours (IQR: 1.5-2.7) at pharmacy visits, substantially longer than what down-referred patient's reported. These results provide support for 'down-referral' and 'task-shifting' to nurse-managed care as a way to improve patient satisfaction and may lead to improved treatment outcomes.

Nurse-managed care has also been estimated to be cost-effective[24]. A recent cost-effectiveness analysis conducted on our same cohort showed that down-referral increased treatment capacity and conserved resources without compromising patient outcomes[39].

Our study is one of the first to evaluate a down-referral model and has several strengths. First, the use of propensity score matching allowed us to minimize confounding[28-30,40]. Second, our ability to link patients lost from care to the South African National Vital Registration Infrastructure Initiative allowed us to more accurately distinguish deaths from losses.

Our findings should be considered alongside its limitations. First, because our study reports on a single government HIV clinic and its associated down-referral site, our results may not be generalizable to the overall population or to PHC settings that lack dedicated space for HIV monitoring and treatment. Second, these results may not necessarily be repeatable in a setting that lacks a data system like TherapyEdge-HIV™. Third, while we matched our study groups on measured predictors of treatment outcomes, there is the potential our populations differed with respect to some unmeasured confounder. However, our sensitivity analysis suggests such an unmeasured confounder would be extremely unlikely our cohort. Fourth, it is possible the rate of loss to follow-up we observed may overstate actual patient attrition since some lost patients may be in care other sites[41]. If this were more common at the treatment-initiation site, the differences in outcomes between our study groups may be less than we observed. Fifth, while the South African National Vital Registration Infrastructure Initiative has been demonstrated to have high sensitivity[42-44], there is a six month delay in updating the registry which could result in misclassification of patients outcomes. Finally, the 548 patients excluded from our analysis for missing data could have introduced selection bias into our results. However, we expect this bias to be minimal since they were similar to patients included in the analysis on observable characteristics.

Conclusion

'Down-referral' of stable ART patients is associated with successful treatment maintenance both in randomized clinical trials and observational data. A large population of stable ART patients at treatment-initiation sites could be down-referred increasing capacity to manage the complications of ART most common during the first six months of treatment. Although 'task-shifting' alone will not solve human resources problems for HIV treatment, it is currently one of the most viable responses to the limited human resources capacity in HIV care. As the body of research assessing the effectiveness of different models of nurse-driven care grows, we are beginning to determine where 'task-shifting' can have the strongest and most sustainable impact. By providing proper equipment, training and support to PHCs and

nurses, large doctor-managed HIV clinics can begin to shift patients to smaller and more accessible nurse-managed PHCs for easier access to HIV care.

Acknowledgments

We express our gratitude to the directors and staff of Themba Lethu Clinic and to Right to Care (RTC), the NGO supporting the study site through a partnership with United States Agency for International Development (USAID). We also thank the Gauteng and National Department of Health for providing for the care of the patients at the Themba Lethu Clinic as part of the Comprehensive Care Management and Treatment plan. Most of all we thank the patients attending the clinic for their continued trust in the treatment provided at the clinic.

Source of Support: Funding was provided by USAID under the terms of agreement 674-A-00-08-00007-00 with Right to Care. Matthew Fox was also supported by Award Number K01AI083097 from the National Institute of Allergy and Infectious Diseases (NIAID). The opinions expressed herein are those of the authors and do not necessarily reflect the views of NIH, NIAID, USAID, the Themba Lethu Clinic or Right to Care.

Appendix 1: Histogram of propensity scores of patients down-referred and not down-referred prior to performing optimal matching in Johannesburg, South Africa (n=3,661)

Appendix 2: Estimates of the effect of down-referral group versus treatment-initiation group on mortality, corrected for an unmeasured confounder for various estimates of the prevalence of the confounder and the effect of the confounder on mortality

Prevalence in		RR (Confounder-Mortality)										
Down-referral Group	Treatment-initiation Site Group	10	10.25	10.5	10.8	11	11.3	11.5	11.75	12	12.25	12.5
0.01	0.45	0.87	0.89	0.90	0.92	0.94	0.95	0.97	0.99	1.01	1.02	1.04
0.06	0.50	0.67	0.68	0.69	0.69	0.70	0.71	0.72	0.73	0.73	0.74	0.75
0.11	0.55	0.56	0.57	0.57	0.58	0.58	0.58	0.59	0.59	0.60	0.60	0.61

Prevalence in		RR (Confounder-Mortality)										
Down-referral Group	Treatment-initiation Site Group	10	10.25	10.5	10.8	11	11.3	11.5	11.75	12	12.25	12.5
0.16	0.60	0.49	0.50	0.50	0.50	0.50	0.51	0.51	0.51	0.52	0.52	0.52
0.21	0.65	0.44	0.45	0.45	0.45	0.45	0.46	0.46	0.46	0.46	0.46	0.47
0.26	0.70	0.41	0.41	0.41	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.43
0.31	0.75	0.38	0.38	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.40
0.36	0.80	0.36	0.36	0.36	0.37	0.37	0.37	0.37	0.37	0.37	0.37	0.37
0.41	0.85	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
0.46	0.90	0.33	0.33	0.33	0.33	0.33	0.34	0.34	0.34	0.34	0.34	0.34
0.51	0.95	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.33	0.33

REFERENCES

1. WHO/UNAIDS/UNICEF. Towards Universal Access: Scaling up priority HIV/AIDS Interventions in the Health Sector. 2010.
2. [revision, 2010] WHO ART for HIV infection in adults and adolescents. Recommendations for a public health approach. [http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf]
3. Curran, J.; Debas, H.; Arya, M.; Kelley, P.; Knobler, S.; Pray, L. Scaling up treatment for the global AIDS pandemic: challenges and opportunities. National Academies Press; Washington: 2005.
4. Dhaliwal, M.; Ellman, T. Improving access to anti-retroviral treatment in Cambodia. International HIV/AIDS Alliance; Brighton: 2003.
5. Gilks C, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet. 2006; 368(9534):505–510. [PubMed: 16890837]
6. World Health Organization. Core Competencies: Results from the International Consensus Meeting on HIV Service Delivery, Training and Certification. Geneva: 2005.
7. World Health Organization. Global Recommendations and Guidelines. Geneva: 2008. Task Shifting: Rational Redistribution of Tasks Among Health Workforce Teams. [<http://www.who.int/healthsystems/TTRTaskShifting.pdf>]
8. Samb B, Celletti F, Holloway J, Van Damme W, De Cock KM, Dybul M. Rapid expansion of the health workforce in response to the HIV epidemic. N Engl J Med. 2007; 357(24):2510–2514. [PubMed: 18077816]
9. National Department of Health. Republic of South Africa. The South African Antiretroviral Treatment Guidelines. 2010. [<http://www.doh.gov.za/docs/factsheets/guidelines/art.pdf>]
10. United States Office of the Global AIDS Coordinator. PEPFAR Report on Workforce Capacity and HIV/AIDS. Washington, DC: 2006.
11. South African National AIDS Council; Technical Task Team (TTT) on Treatment, Care & Support. Building the capacity of the primary health care system for HIV/AIDS diagnosis, care and treatment in South Africa: Task Shifting Recommendations Document. Apr.2010 Vol. 100(No. 4 SAMJ)
12. Zachariah R, Ford N, Philips M, Lynch S, Massaquoi M, Janssens V, Harries D. Task shifting in HIV/AIDS: opportunities, challenge and proposed actions for sub-Saharan Africa. Trans R Soc Trop Med Hyg. 2009; 103:549–558. [<http://www.ncbi.nlm.nih.gov/pubmed/18992905>]. [PubMed: 18992905]
13. Lehmann U, Van Damme W, Barten F, Sanders D. Task shifting: the answer to the human resources crisis in Africa? Human Resources for Health. 2009; 7:49. [<http://www.ncbi.nlm.nih.gov/pubmed/19545398>]. [PubMed: 19545398]
14. Sanne I, Orrell C, Fox MP, Conradie F, Ive P, Zeinecker J, Cornell M, Heiberg C, Ingram C, Panchia R, Rassool M, Gonin R, Stevens W, Truter H, Dehlinger M, van der HC, McIntyre J,

Wood R. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. *Lancet*. 2010; 376:33–40. [PubMed: 20557927]

15. Jaffar S, Amuron B, Foster S, Birungi J, Levin J, Namara G, Nabiryo C, Ndembu N, Kyomuhangi R, Opio A, Bunnell R, Tappero JW, Mermin J, Coutinho A, Grosskurth H. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster randomised equivalence trial. *Lancet*. 2009; 374:2080–2089. [[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(09\)61674-3](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61674-3)]. [PubMed: 19939445]
16. Vasana, A.; Kenya-Mugisha, N.; Seung, KJ.; Achieng, M.; Banura, P.; Lule, F.; Beems, M.; Todd, J.; Madraa, E. Agreement between physicians and non-physician clinicians on starting antiretroviral therapy in rural Uganda. *Human Resources for Health*. Aug 20. 2009 DOI: 10.1186/1478-4491-7-75. <http://www.ncbi.nlm.nih.gov/pubmed/19695083>
17. Sherr K, Pfeiffer J, Mussa A, et al. The role of non-physician clinicians in the rapid expansion of HIV care in Mozambique. *J Acquir Immune Defic Syndr*. 2009; 52:S20–S23. <http://www.ncbi.nlm.nih.gov/pubmed/19858931>.
18. Gimbel-Sherr SO, Micek MA, Gimbel-Sherr KH, et al. Using nurses to identify HAART eligible patients in the Republic of Mozambique: results of a time series analysis. *Human Resources for Health*. 2007; 28(5):7. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1817650>.
19. Humphreys CP, Wright J, Walley J, Mamvura CT, Bailey KA1, Ntshalintshali SN, West RM, Philip A. Nurse led, primary care based antiretroviral treatment versus hospital care: a controlled prospective study in Swaziland. *BMC Health Services Research*. 2010; 10:229. [PubMed: 20687955]
20. Sherr KH, Micek MA, Gimbel SO, Gloyd SS, Hughes JP, John-Stewart GC, Manjate RM, Pfeiffer J, Weiss NS. Quality of HIV care provided by non-physician clinicians and physicians in Mozambique: a retrospective cohort study. *AIDS*. Jan 24.2010 (Suppl 1):S59–66. [PubMed: 20023441]
21. Decroo T, Panunzi I, das Dores C, Maldonado F, Biot M, Ford N, Chu K. Lessons learned during down referral of antiretroviral treatment in Tete, Mozambique. *J Int AIDS Soc*. May 6.2009 12(1): 6. [PubMed: 19419543]
22. Laurant M, Reeves D, Hermens R, Braspenning J, Grol R, Sibbald B. Substitution of doctors by nurses in primary care. *Cochrane Database of Systematic Reviews*. 2004
23. Wilson IB, et al. Quality of HIV care provided by nurse practitioners, physician assistants, and physicians. *Ann Intern Med*. 2005; 143(10):729–36. [PubMed: 16287794]
24. Callaghan M, Ford N, Schneider H. A systematic review of task-shifting for HIV treatment and care in Africa. *Hum Resource Health*. 2010; 8:8.
25. Brinkhof M, Dabis F, Myer L, Bangsberg D, Boule A, Nash D, Schechter M, Laurent C, Keiser O, May M, Sprinz E, Egger M. Anglaret X for the ART-LINC of IeDEA collaboration: Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. *Bull World Health Organ*. 2008; 86:559–67. [PubMed: 18670668]
26. Fatti G, Grimwood A, Bock P. Better antiretroviral therapy outcomes at primary healthcare facilities: an evaluation of three tiers of ART services in four South African provinces. *PLoS One*. 2010; 5:e12888. [PubMed: 20877631]
27. National Department of Health. Republic of South Africa. National Antiretroviral Treatment Guidelines. Jacana Publishers; 2004. 2004
28. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983; 70:41–55.
29. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997; 127(8 pt 2):757–763. pmid:9382394. [PubMed: 9382394]
30. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol*. 1999; 150:327–333. pmid:10453808. [PubMed: 10453808]
31. DIST and NOBS macro designed for optimal case-control matching. Erik Bergstralh & Jon Kosanke. Nov 27. 2003 Available at <http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm>

32. Fairall LR, Bachmann MO, Louwagie GM, van Vuuren C, Chikobvu P, Steyn D, et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. *Arch Intern Med.* 2008; 168:86–93. [PubMed: 18195200]
33. Fox MP, Brennan A, Maskew M, MacPhail P, Sanne I. Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa. *Trop Med Int Health.* 2010; 15(4):405–413. [PubMed: 20180931]
34. Boule A, Van Cutsem G, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. *AIDS.* 2010; 24(4):563–572. [PubMed: 20057311]
35. Greenland, S. Basic methods for sensitivity analysis and external adjustment. In: Rothman, KJ.; Greenland, S., editors. *Modern epidemiology.* 2nd edn. Lippincott-Raven; Philadelphia, PA: 1998. p. 343–58.
36. Lash, TL.; Fox, MP.; Fink, AK. *Applying Quantitative Bias Analysis to Epidemiologic Data.* Springer; 2009.
37. Fairall, Lara R.; Bachmann, Max O.; Zwarenstein, Merrick F.; Lombard, Carl J.; Uebel, Kerry; van Vuuren, Cloete; Steyn, Dewald; Boule, Andrew; Bateman, Eric D. Streamlining tasks and roles to expand treatment and care for HIV: randomised controlled trial protocol. *Trials.* 2008; 9:21. [PubMed: 18433494]
38. Colvin, Christopher J.; Fairall, Lara; Lewin, Simon; Georgeu, Daniella; Zwarenstein, Merrick; Bachmann, Max; Uebel, Kerry E.; Bateman, Eric D. Expanding access to ART in South Africa: The role of nurseinitiated treatment. *South African Medical Journal.* 2010; Vol 100(No 4)
39. Long L, Brennan A, Fox M, Ndibongo B, Jaffray I, Maskew M, MacPhail P, Sanne I, Rosen S. Treatment Outcomes and Cost-Effectiveness of Shifting Management of Stable ART Patients to Nurses in South Africa: An Observational Cohort. *PLoS Medicine.* Jul.2011 8:7.
40. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Statist. Med.* 2008; 27:2037–2049.
41. Geng EH, Nash D, Kambugu A, Zhang Y, Braitstein P, Christopoulos KA, Muyindike W, Bwana MB, Yiannoutsos CT, Petersen ML, Martin JN. Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions. *Curr HIV /AIDS Rep.* 2010; 7:234–44. [PubMed: 20820972]
42. Statistics South Africa. Mortality and causes of death in South Africa, 1997-2003. Findings from death notification. P0309.3. 2005.
43. Dorrington, R.; Bourne, D.; Bradshaw, D.; Laubsher, R.; Timaeus, I. The impact of HIV/AIDS on adult mortality in South Africa. Medical Research Council; Cape Town: 2001.
44. Timaeus, I.; Dorrington, R.; Bradshaw, D.; Nannan, N. Mortality trends in South Africa 1985-2000: From apartheid to AIDS. South African Medical Research Council; Cape Town: 2002.

Figure 1. Selection of study patients for an analysis of the effects of down-referral of stable HIV treatment patients in Johannesburg, South Africa
 d4T, stavudine; 3TC, lamivudine; LPRr, lopinavir/ritonavir; AZT, zidovudine; ddI, didanosine

Table 1

Predictors of down-referral among stable ART patients prior to matching at the Themba Lethu Clinic in Johannesburg, South Africa * (n=3,661)

Predictor variable at down-referral eligibility		Down-referred (n=693) (n, %)	Not Down-referred (n=2968) (n, %)	Odds Ratio [€] (95% CI)
Gender	Male	241 (34.6%)	1028 (34.6%)	1.0
	Female	452 (65.4%)	1940 (65.4%)	0.99 (0.82-1.19)
Age (years)	50	72 (10.4%)	312 (10.5%)	1.0
	40-49.9	192 (27.7%)	817 (27.5%)	1.07 (0.79-1.45)
	30-39.9	343 (49.5%)	1466 (49.4%)	1.06 (0.80-1.42)
	25-29.9	66 (9.5%)	304 (10.2%)	1.02 (0.69-1.50)
	18-24.9	20 (2.9%)	69 (2.4%)	1.35 (0.75-2.42)
CD4 category	200-299 cells/mm ³	128 (18.4%)	862 (29.0%)	1.0
	300-399 cells/mm ³	206 (29.7%)	859 (28.9%)	1.49 (1.17-1.90)
	400-499 cells/mm ³	151 (21.9%)	546 (18.5%)	1.72 (1.32-2.25)
	500 cells/mm ³	208 (30.0%)	701 (23.6%)	1.75 (1.35-2.26)
Body Mass Index	<17.5	9 (1.3%)	62 (2.1%)	1.0
	17.5	684 (98.7%)	2906 (97.9%)	1.66 (0.81-3.39)
Haemoglobin	<10.0	11 (1.6%)	95 (3.2%)	1.0
	10.0	682 (98.4%)	2873 (96.8%)	2.02 (1.07-3.83)
Time on ART (months)	10-17.9	148 (21.5%)	1025 (34.5%)	1.0
	18-23.9	126 (18.2%)	482 (16.2%)	1.72 (1.32-2.24)
	24-29.9	109 (15.7%)	399 (13.4%)	1.79 (1.35-2.36)
	30-35.9	102 (14.7%)	360 (12.1%)	1.85 (1.39-2.47)
	36-41.9	98 (14.1%)	433 (14.6%)	1.43 (1.07-1.92)
	42-47.9	100 (14.4%)	242 (8.2%)	2.62 (1.93-3.55)
	48-53.9	10 (1.4%)	27 (1.0%)	2.87 (1.32-6.24)
AZT- vs. d4T-based regimen	AZT	209 (30.1%)	997 (33.6%)	1.0
	d4T	484 (69.9%)	1971 (66.4%)	1.23 (1.02-1.49)
EFV- vs. NVP-based regimen	EFV	61 (8.8%)	242 (8.4%)	1.0
	NVP	632 (91.2%)	2630 (91.6%)	1.05 (0.78-1.43)
Age (years)	mean (SD)	36.3 (8.2)	36.7 (8.3)	36.3 (8.3)
CD4 category	mean (SD)	440.5 (165.2)	408.3 (169.4)	414 (169.0)
Body Mass Index	mean (SD)	24.9 (4.5)	24.8 (4.6)	24.8 (4.6)
Haemoglobin	mean (SD)	14.1 (1.7)	13.7 (1.8)	13.8 (1.8)
Time on ART (months)	mean (SD)	31.3 (11.4)	27.8 (11.9)	28.5 (11.9)

[€] Odds ratios calculated from a logistic regression model; predicted probabilities were used to create propensity scores to match patients for analyses of outcomes after down-referral.

* d4T = stavudine, EFV = efavirenz, NVP = nevirapine, AZT = zidovudine

Table 2

Patient characteristics at down-referral eligibility and outcomes by 12-months of follow-up amongst HIV treatment patients in Johannesburg, South Africa after propensity score matching (n=2,772)

		Down-referral Status		
Characteristics		Down-referred (n=693)	Not Down- referred (n=2079)	Total (n=2772)
Sex	Female	452 (65.2)	1369 (65.8)	1821 (65.7)
	Male	241 (34.8)	710 (34.2)	951 (34.3)
CD4 count at down-referral eligibility	200-299 cells/mm ³	128 (18.5)	458 (22.0)	586 (21.1)
	300-399 cells/mm ³	206 (29.7)	688 (33.1)	894 (32.3)
	400-499 cells/mm ³	151 (21.8)	418 (20.1)	569 (20.5)
	500 cells/mm ³	208 (30.0)	515 (24.8)	723 (26.1)
ART regimen at down-referral eligibility	d4T-3TC-EFV	441 (63.5)	1354 (65.1)	1795 (64.8)
	AZT-3TC-EFV	191 (27.6)	557 (26.8)	748 (27.0)
	d4T-3TC-NVP	44 (6.4)	111 (5.3)	155 (5.6)
	AZT-3TC-NVP	17 (2.5)	54 (2.7)	71 (2.5)
	AZT-3TC-LPVr	0 (0.0)	3 (0.1)	3 (0.1)
Year initiated on ART	2004	148 (21.4)	438 (21.1)	586 (21.1)
	2005	192 (27.7)	597 (28.7)	789 (28.5)
	2006	240 (34.6)	689 (33.1)	929 (33.5)
	2007	111 (16.0)	348 (16.8)	459 (16.6)
	2008	2 (0.3)	7 (0.3)	9 (0.3)
Tuberculosis at ART initiation	Yes	104 (15.0)	362 (17.4)	466 (16.8)
	No	589 (85.0)	1717 (82.6)	2306 (83.2)
WHO Stage	I/II	396 (57.1)	1167 (56.1)	1563 (56.4)
	III	254 (36.7)	792 (38.1)	1046 (37.7)
	IV	43 (6.2)	120 (5.8)	163 (5.9)
Valid South African national identification number	Yes	502 (72.4)	1533 (73.7)	2035 (73.4)
	No	191 (27.6)	546 (26.3)	737 (26.6)
CD4 count (cells/mm ³) at down-referral eligibility	Median (IQR)	406 (324-528)	383 (307-498)	389 (311-507)
CD4 count (cells/mm ³) at ART initiation	Median (IQR)	108 (43-168)	101 (40-168)	102 (41-168)
Months on ART prior to down-referral eligibility	Median (IQR)	28.7 (19.7-38.7)	30.0 (24.0-42.0)	30.0 (22.3-42.0)
Months from ART initiation to viral load suppression	Median (IQR)	3.9 (3.6-5.0)	3.9 (3.6-5.4)	3.9 (3.6-5.3)
Single drug substitutions from ART initiation to down-referral eligibility	Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)
Hemoglobin (ug/dL)	Median (IQR)	14.1 (13.1-15.2)	13.8 (12.9-14.9)	13.9 (12.9-15.0)
Body Mass Index	Median (IQR)	24.4 (21.9-27.8)	24.0 (21.5-27.5)	24.1 (21.6-27.6)
Age	Median (IQR)	35.2 (31.0-40.7)	35.2 (30.7-41.8)	35.3 (30.8-41.6)
12-month outcomes				
Death	n (%)	2 (0.3)	32 (1.5)	34 (1.2)
Loss to follow-up	n (%)	10 (1.4)	87 (4.2)	97 (3.5)

Down-referral Status				
Characteristics		Down-referred (n=693)	Not Down- referred (n=2079)	Total (n=2772)
Transferred	n (%)	0 (0.0)	2 (0.1)	2 (0.1)
Alive and in care	n (%)	681 (98.3)	1958 (94.2)	2639 (95.2)
Viral load rebound by 12-months	Yes	22 (3.3)	100 (5.6)	122 (5.0)
	No	654 (96.8)	1674 (94.4)	2328 (95.0)
CD4 count increase by 12-months (cells/mm ³)	Median (IQR)	55 (-24-127)	59 (-12-146)	58 (-15-140)

ART, antiretroviral therapy; IQR, interquartile range; d4T, stavudine; 3TC, lamivudine; EFV, efavirenze; AZT, zidovudine; NVP, nevirapine; LPVr, lopinavir/ritonavir

Table 3

Predictors of loss to follow-up, mortality and viral load rebound by down-referral status and amongst HIV treatment patients in Johannesburg, South Africa (n=2,772)

	No. Events (%)	Person Time (years)	Rate (per 100 person yrs.)	Adjusted HR [†] (95% CI)	No. Events (%)	Person Time (years)	Rate (per 100 person yrs.)	Adjusted HR [†] (95% CI)	No. Events (%)	Adjusted RR [§] (95% CI)
Mortality [£]										
Loss to follow-up [‡]										
Viral load rebound [€]										
Down referral status										
Not down-referred	32 (1.5)	2025.6	1.6	Reference	87 (4.2)	2025.6	4.3	Reference	100 (5.6)	Reference
Down-referred	2 (0.3)	687.7	0.3	0.2 (0.04-0.8)	10 (1.4)	687.7	1.5	0.3 (0.2-0.6)	22 (3.3)	0.6 (0.4-0.9)
Gender										
Female	21 (1.2)	1787.6	1.2	Reference	69 (3.8)	1787.6	3.9	Reference	74 (4.6)	Reference
Male	13 (1.4)	931.8	1.4	1.1 (0.5-2.3)	28 (2.9)	931.8	3.0	0.8 (0.5-1.3)	48 (5.7)	1.3 (0.9-1.9)
Age (years)										
50	6 (2.8)	209.6	2.9	Reference	5 (2.3)	209.6	2.4	Reference	5 (2.6)	Reference
40-49.9	10 (1.6)	613.9	1.6	0.6 (0.2-1.6)	14 (2.2)	613.9	2.3	0.9 (0.3-2.3)	25 (4.6)	1.9 (0.7-4.9)
30-39.9	11 (0.8)	1306.6	0.8	0.3 (0.1-0.9)	43 (3.2)	1306.6	3.3	1.3 (0.5-3.0)	57 (4.7)	1.9 (0.8-4.7)
25-29.9	6 (1.4)	429.5	1.4	0.6 (0.2-1.8)	22 (5.0)	429.5	5.1	1.9 (0.8-4.7)	27 (7.2)	3.1 (1.2-8.0)
18-24.9	1 (0.7)	148.2	0.7	0.3 (0.04-3.0)	12 (7.8)	148.2	8.1	3.1 (1.1-8.6)	8 (6.0)	2.6 (0.8-8.2)
CD4 count										
500 cells/mm ³	8 (1.1)	708.4	1.1	Reference	19 (2.6)	708.4	2.7	Reference	24 (3.7)	Reference
400-499 cells/mm ³	4 (0.7)	557.4	0.7	0.7 (0.2-2.2)	21 (3.7)	557.4	3.8	1.4 (0.7-2.5)	25 (5.0)	1.3 (0.7-2.2)
300-399 cells/mm ³	12 (1.3)	875.3	1.4	1.1 (0.5-2.8)	35 (3.9)	875.3	4.0	1.6 (0.9-2.8)	38 (4.8)	1.3 (0.8-2.1)
200-299 cells/mm ³	10 (1.7)	572.2	1.7	1.5 (0.6-3.8)	22 (3.8)	572.2	3.8	1.5 (0.8-2.9)	35 (6.8)	1.7 (1.0-2.9)
AZT- vs. d4T-based regimen at down-referral eligibility										
AZT	11 (1.4)	801.9	1.4	Reference	21 (2.6)	801.9	2.6	Reference	26 (3.6)	Reference
d4T	23 (1.2)	1911.5	1.2	0.8 (0.4-1.8)	76 (3.9)	1911.5	4.0	1.4 (0.8-2.2)	96 (5.6)	1.4 (0.9-2.1)
NVP- vs. EFV-based regimen at down-referral eligibility										
EFV	32 (1.3)	2485.5	1.3	Reference	89 (3.5)	2485.5	3.6	Reference	110 (4.9)	Reference
NVP	2 (0.9)	219.9	1.0	0.9 (0.2-3.9)	8 (3.6)	219.9	3.6	0.8 (0.4-1.7)	12 (6.0)	1.2 (0.7-2.2)
Valid South African national identification number										
No	6 (0.8)	720.0	0.8	Reference	34 (4.6)	720.0	4.7	Reference	36 (5.6)	Reference

[†]Hazard ratios (HR) are from a Cox proportional regression models

[§]Relative risks (RR) are from log-linear regression models

[¥]Loss to follow-up was defined as >4 months since last visit

[£]Deaths are reported to the clinic by the hospital or the patients family notifying the clinic staff, the counselors identify the death through active tracing or through linkage with the South African National Vital Registration Infrastructure Initiative for those loss to follow-up

[€]Viral load rebound was defined as having an unsuppressed viral load at 12-months after being suppressed at down-referral eligibility

All variables adjusted for in the models are listed in the table

CI, confidence interval; AZT, zidovudine; d4T, stavudine; NVP, nevirapine; EFV, lamivudine