ORIGINAL RESEARCH ARTICLE

Good treatment outcomes among foreigners receiving antiretroviral therapy in Johannesburg, South Africa

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Summary: Foreigners, including displaced persons, often have limited health-care access, especially to HIV services. Outcomes of antiretroviral therapy (ART) in South Africans and foreigners were compared at a Johannesburg non-governmental clinic. Records were reviewed of 1297 adults enrolled between April 2004 and March 2007 (568 self-identified foreigners, 431 South Africans citizens and 298 with unknown origin). Compared with citizens, foreigners had fewer hospital admissions (39%, 90/303 versus 51%, 126/244; $P < 0.001$), less missed appointments for ART initiation (20%, 39/200 versus 25%, 51/206; $P < 0.001$), faster median time to ART initiation (14 versus 21 days, $P = 0.008$), better retention in care (88%, 325/369 versus 69%, 155/226; $P < 0.001$) and lower mortality (2.5%, 14/568 versus 10%, 44/431; $P < 0.001$) after 426 person-years. In logistic regression, after controlling for baseline CD4 count and tuberculosis status, foreigners were 55% less likely to fail ART than citizens (95% CI = 0.23–0.87). These findings support United Nations High Commissioner for Refugees recommendations that ART should not be withheld from displaced persons.

Keywords: antiretroviral therapy, South Africa, refugees, HIV, UNHCR

INTRODUCTION

Declining and disparate economic conditions, armed conflict and political uncertainty all have culminated in the migration of considerable millions of people in sub-Saharan Africa in the past decade.[1] Since the end of apartheid, South Africa has become a primary destination for migrants from neighbouring countries and beyond, a number of whom are refugees and asylum seekers.[2] With more than 251,000 asylum applications since 2002, this country is one of the largest asylum recipients in the world, second only to the USA in terms of new claims in 2007.[1] The level of undocumented migrants is, however, much higher, though no official statistics exist. Popular press estimates of the numbers of Zimbabweans living in South Africa, for example, range from several hundred thousands to four million.[3]

The South African government has adopted an integrative asylum policy for managing refugees entering the country.[4,5] Refugees are therefore expected to become self-sufficient (i.e. obtain employment and housing) and make use of the social services available to the local population.[6] However, this is contingent on obtaining official documentation of refugee status, which is limited by ineffectual systems and available only in a few major centres. At the end of 2007, South Africa had the world's largest number of pending asylum applications (171,000).[1] Most often, in effect, refugees and other foreigners are unable to integrate. This may have contributed to the xenophobic violence seen in mid-2008 across South Africa.[7]

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In many countries, the health-care needs of foreigners are inadequately provided for by their adoptive countries.[2,8–10] In South Africa, public sector provision of antiretroviral therapy (ART) was initially restricted to holders of South African identity documents. Such policies have also been implemented in other countries, partly in the belief that 'high mobility amongst these categories of people [displaced and homeless people] prohibits good adherence'.[11] Following pressure from civil society, directives from the South African Department of Health reversed these legislative obstacles to ART access for foreigners.[12–14] However, health facilities are reportedly slow to conform to the government's directive[6,15] and foreigners continue to have limited public sector access to ART and HIV care. Eligibility for ART was not contingent on citizenship in the non-government sector in South Africa, which like the public services began a large scale up of ART in 2004.

Evidence showing that ART outcomes among foreigners are comparable with that of local residents may renew efforts to ensure equal access to ART for all population groups, both in South Africa and in similar settings. This paper compares outcomes of ART in foreigners with that of South Africa citizens, using data from an ART clinic in a non-governmental facility.

METHODS

Study site

Nazareth House, a faith-based organization in Yeoville, Johannesburg is one of the 14 sites funded by the South African Catholic Bishop's Conference and the Presidential Emergency Plan for AIDS Relief to provide ART.

Johannesburg has a population of nearly 3.9 million, an estimated 6.2% of whom are international migrants.[16] In particular, the inner city suburbs, such as Yeoville, have high concentrations of foreigners and newly urbanized peoples.[6,17] From 2004 onwards, adults and children attending Nazareth House outpatient clinic or the inpatient HIV hospice received clinical and laboratory management of HIV infection, according to South African ART guidelines. No user fees were charged and formal identity documentation or residence status was not required to receive services. Follow-up of defaulting clients was largely passive, done by a community-based organization.

Record review

In March 2007, an audit team comprising doctors, professional nurses and lay-community workers conducted a record-review over five consecutive days. A standardized data collection form was used to review records of all clients enrolled at the HIV clinic. Data were extracted on demographics, clinic and hospice attendance, clinical and laboratory monitoring of HIV disease, opportunistic infections and current health status. For quality control, all completed audit forms were reviewed by a senior member of the audit team. Approval for the record review was given by Human Research Ethics Committee of the University of the Witwatersrand, protocol number M080609.

Study variables

Participants were defined as 'citizens' if it was recorded in clinical notes that the client self-identified as South African, while clients who self-identified as being of non-South African origin were defined as foreigners.

Failure of ART was defined as the presence of any of the following criteria: ART cessation, patient death, a plasma viral load >1000 copies/mL or any decrease in CD4 count from pre-ART levels. Conversely, patients were considered to have an adequate response to ART if they had none of the above failure criteria, had received ART for more than six months at the time of audit and had viral suppression <50 copies/mL or any increase in CD4 cell count from baseline.

Data management and analysis

Data were entered into a Microsoft Access 2004 database and analysed using Intercooled Stata version 8.0 (College Station, TX, USA). Data analysis included descriptive and summary statistics, chi-square tests to detect associations between categorical variables and unpaired Student's *t*-tests for analysis of continuous variables. Analysis of covariance was used to examine differences between the study groups in CD4 counts at six, 12 and 18 months. This analysis adjusted for effects of baseline CD4 cell count values and square-root transformation was applied to CD4 cell counts, as commonly performed.[18]

The characteristics of patients with known and unknown citizenship status were compared and analysis thereafter was restricted to people with known citizenship status. It was deemed inappropriate to use the available data on a participant to impute statistically plausible values, or to use inverse probability weighting to deal with incomplete data.[19,20] As shown in another local study,[21] and in other sites,[22] attrition in ART programmes is mostly non-random and dependent on unobserved data.

A multivariate logistic regression model assessed whether treatment outcome was associated with citizenship status, after controlling for potential confounding variables. Variables associated with treatment outcome in univariate analysis were included in the initial multivariate model and retained if their removal markedly altered the model's fit.

RESULTS

Demographics and HIV disease

From April 2004 until March 2007, 1297 adults (≥16 years) were enrolled at the clinic of whom 568 (44%) self-identified as foreigners and 431 (33%) as citizens. In the clinical notes of 298 (23%) people, no country of origin was recorded. Of those who were foreign, about two-thirds were from Zimbabwe (376), with the remainder from Zambia (42), Malawi (36), Mozambique (27), Nigeria (15), the Great Lakes region (14), other African countries (39) and 19 were foreigners of unknown origin.

Female subjects predominated in all study groups (South Africans, foreigners and those of unknown citizenship; Table 1). Person-years of observation totalled 552, with a similar duration for citizens and foreigners. No difference was detected in the baseline CD4 cell count between citizens and foreigners at initiation of ART. However, compared with citizens, foreigners had fewer admissions to inpatient facilities (odds ratio [OR] = 0.40; 95% confidence interval [CI] = 0.28–0.57), and a smaller proportion previously had tuberculosis (TB) (OR = 0.79; 95% CI = 0.61–1.0) or cryptococcal disease (OR = 0.32; 95% CI = 0.12–0.84). Two cases of Kaposi's sarcoma were detected in foreigners.

Differences in gender and baseline CD4 cell count were detected between those with a known and unknown citizenship status. The unknown group were also less likely to initiate ART, and those who did had longer delays between first clinic attendance and ART initiation.

Antiretroviral therapy

A higher proportion of foreigners initiated ART, even after controlling for differences in baseline CD4 cell count (OR = 1.4, 95% CI = 1.0–1.9; $P = 0.07$). This difference was mainly due to fewer missed appointments (39 in foreigners versus 50 in citizens) and death (17 versus 8). Foreigners had a faster median time between clinic entry and ART initiation (14 days versus 21 days for citizens, $P = 0.008$). Eighty-three percent (290/350) of foreigners were initiated on the recommended first-line ART regimen in South Africa (stavudine, lamivudine and efavirenz) compared with 92% of citizens (190/207; $P = 0.003$).

Among all participants (those receiving and not receiving ART), fewer foreigners died (2.5%, 14/568 versus 10% of South Africans, 44/431; $P < 0.001$: Table 2). More foreigners than citizens had viral suppression and/or CD4 increase at the end of the study period ($P < 0.001$). No difference was detected in median CD4 count among citizens and foreigners in follow-up CD4 cell count measures. Side-effect profiles (data not shown) and the proportion of clients requiring regimen change among citizens and foreigners were similar. Proportionately more foreigners were retained in care at March 2007 compared with citizens (88%, 325/368 versus 69%, 155/226; $P < 0.001$). Of those who initiated ART, a higher proportion of citizens than foreigners had stopped ART (8%, 17/226 versus 4%, 16/368), was unaccounted for (4%, 8/226 versus 2%, 9/368), had died (9%, 21/226 versus 1%, 5/369) or had been transferred to another HIV care centre (12%, 25/226 versus 4%, 14/369).

Table 1 **Demographic, clinical and immunological characteristics of patients enrolled at Nazareth House HIV Clinic between April 2004 and March 2007**

Variable	Entire cohort (n = 1297)	A. Foreign citizens (n = 568)	B. SA citizens (n = 431)	C. Not known (n = 298)	P A vs B	P (A + B) vs C
Demographics and clinical history						
Age mean (SD)	36.3 (8.9)	36.0 (8.0)	37.1 (9.4)	34.4 (9.6)	0.04	0.25
Female n/No. (%)	819/1275 (64)	322/563 (57)	290/427 (68)	207/285 (73)	0.001	0.001
Person-years observed at clinic	552	209	217	125		
Opportunistic infections before ART n/No. (%)						
TB, all forms	486/1297 (37)	206/568 (36)	180/431 (42)	100/298 (34)	0.077	0.11
Bacterial pneumonia	63/1297 (5)	37/568 (7)	18/431 (4)	8/298 (3)	0.11	0.05
Cryptococcosis	24/1297 (2)	6/568 (1)	14/431 (3)	4/298 (1)	0.014	0.46
Kaposi's sarcoma	17/1297 (1)	14/568 (2)	2/431 (0)	1/298 (0)	0.01	0.09
Admissions to inpatient facility before ART n/No. (%)	272/691 (39)	90/303 (30)	126/244 (51)	56/1440 (39)	<0.001	0.90
ART initiation						
Initiation on ART n/No. (%)						
Initiated on ART at clinic	436/1297 (34)	235/568 (41)	137/431 (32)	64/298 (21)		
Initiated elsewhere (presenting on ART)	258/1297 (20)	134/568 (24)	90/431 (21)	34/298 (11)		
Not initiated on ART	603/1297 (46)	199/568 (35)	204/431 (47)	200/298 (67)	<0.001	<0.001
Reason not initiated on ART n/No. (%)						
Not eligible as CD4 >200	173/606 (29)	61/200 (31)	57/206 (28)	55/200 (28)		
Missed appointment	155/606 (26)	39/200 (20)	51/206 (25)	65/200 (33)		
Death	36/606 (6)	8/200 (4)	17/206 (8)	11/200 (6)		
Still in pre-ART counselling	34/606 (6)	26/200 (13)	6/206 (3)	2/100 (1)		
Other reason	32/606 (5)	9/200 (5)	14/206 (7)	9/200 (5)		
Unknown reason	176/606 (29)	57/200 (29)	61/206 (30)	58/200 (29)	0.002	0.004
CD4 cell count at ART initiation at clinic: median cells/mm^3 (IQR); n	87 (35–147); 359	81 (31–146); 205	109.5 (49.5–157.5); 104	69 (32–127); 50	0.60	0.002
Time from clinic enrolment to ART initiation: median days (IQR); n	16.5 (7–49); 528	14 (7–35); 270	21 (7–58); 175	22 (7–72); 83	0.008	0.007

ART = antiretroviral therapy; TB = tuberculosis; IQR = interquartile range; SD = standard deviation

Patients with an unknown citizenship status had high levels of mortality (11%, 32/298), and of viral detection and/or immunological failure (53%, 42/78).

In univariate analysis, several factors were associated with failure after at least six months ART (Table 3), namely South African citizenship; TB or cryptococcal disease before ART; initiation outside Nazareth House; any hospital admission; and having initiated ART in 2004 (the first year of the programme). In multivariate analysis, citizenship status, baseline CD4 cell count and previous TB disease were retained in the final model. Those with previous TB were 2.5 times more likely to fail ART (95% CI = 1.4–4.5). Foreigners were about half as likely to fail ART as citizens (adjusted odds ratio [AOR] = 0.45, 95% CI = 0.23–0.87; P = 0.017).

DISCUSSION

This article provides, to our knowledge, the first evidence that foreigners have sustained short to mid-term benefit from HIV services in an African country. In this cohort, foreigners have fewer missed opportunities for ART initiation, faster initiation on ART, better retention in care, better response to ART after six months, and importantly, lower mortality when compared with citizens receiving care in the same setting.

In our cohort, the foreigners had lower baseline median CD4 cell counts, similar to levels seen in cohorts in similar settings[18,23] However, after 148 person-years observation, the treatment outcome was unknown for only 2% of foreigners, notably lower than in other cohorts. For example, HIV programmes with passive follow-up in four sites in developing countries in a similar time period reported that 19% of clients were unaccounted for after one year of ART.[23]

The spectrum of opportunistic disease among citizens and foreigners differed: South Africans had more cases of TB and cryptococcosis, while Kaposi's sarcoma was more frequent in foreigners. These observations likely reflect the geographical distribution of infectious agents on the continent: TB in South Africa has a reported incidence of 940 cases/100,000[24] higher than Zimbabwe (557 cases/100,000), Zambia (553/100,000) and Malawi (377/100,000).[25] Kaposi's sarcoma is traditionally associated with eastern and central Africa,[26] while recent evidence demonstrates the high burden of cryptococcosis in southern Africa.[27]

Fewer missed opportunities for ART initiation among foreigners, and faster time to initiation on ART may suggest a greater degree of tenacity and determination to obtain health care in this group. Moreover, the natural history of HIV disease may differ in foreigners. Migration may select for HIV-infected individuals who are relatively healthier than their local counterparts. Also, evidence suggests that refugees often have lower HIV prevalence than host populations, though it is unknown whether that finding applies to all groups of international migrants.[28] Differences in underlying HIV disease may account for the lower mortality among foreigners. Conversely, fewer hospitalizations and relatively low CD4 count responses might reflect disparate access to health care and poorer socioeconomic conditions in their adoptive country.

The good response to ART among foreigners in this cohort is particularly surprising given the obstacles they encounter in living in inner city Johannesburg and in adhering to ART.[15] Another report has described barriers among foreigners, including early referral out of public-sector HIV treatment programmes, lack of transport money to collect medication, difficulties with taking time away from their livelihood activities and inability to access government-sponsored disability grants.[15] In addition, an

Table 2 **Outcomes of antiretroviral therapy of clients enrolled at Nazareth House HIV Clinic April 2004–March 2007**

Variable	A. Foreign citizens	B. SA citizens	C. Not known	*P* A vs B	*P* (A + B) vs C
Person-years observation on ART total; median (IQR)	187.6; 0.5 (0.1–0.9)	148.1; 0.6 (0.2–1.1)	59.7; 0.5 (0.2–1.1)	<0.008	0.87
Treatment outcome *n*/No. (%)					
Viral suppression and/or CD4 increase	135/178 (76)	83/143 (58)	36/78 (46)		
Viral detection and/or CD4 cell decrease	43/178 (24)	60/143 (42)	42/78 (53)	0.001	<0.001
Immunological failure at any time during ART *n*/No. (%)*	16/147 (11)	14/91 (15)	15/58 (26)	0.31	0.012
CD4 cell count† median cells/mm³ (IQR); *n*					
After 6 months of ART	210 (119–305); 98	230 (121–300); 53	216 (150–256);24	0.77	
After 12 months of ART	249 (157–353); 116	316 (164–457); 82	246 (153–388); 42	0.22	
After 18 months of ART	248 (155–351); 121	304 (164–457); 83	246 (153–388); 42	0.20	
Change in CD4 count after ART initiation†					
After 6 months median cells/mm³ (IQR); *n*	103 (50–178); 80	137 (80–189); 40	117 (54–164); 15	0.94	
After 12 months median cells/mm³ (IQR); *n*	151 (79–244); 79	215 (109–293); 55	178 (109–261); 28	0.34	
Regimen change *n*/No. (%)	37/369 (10)	23/226 (10)	6/98 (6)	0.95	0.22
Current status on therapy *n*/No. (%)					
Currently receiving treatment	325/369 (88)	155/226 (69)	63/98 (64)		
Transferred out	14/369 (4)	25/226 (11)	12/98 (12)		
Died	5/369 (1)	21/226 (9)	11/98 (11)		
Unaccounted for (defaulter)	9/369 (2)	8/226 (4)	1/98 (1)		
ART stopped	16/369 (4)	17/226 (8)	11/98 (11)	<0.001	0.001
Tuberculosis after ART initiation *n*/No. (%)	13/369 (4)	10/226 (4)	4 (4/98)	0.58	0.92
Death (in those receiving and not receiving ART) *n*/No. (%)	14/568 (2.5)	44/431 (10)	11 (32/298)	<0.001	0.001

*Failure of ART was defined as the presence of any of the following criteria: ART cessation, patient death, a plasma viral load >1000/ml or any decrease in CD4 count from pre-ART levels

†Analysis of covariance, adjusting for baseline CD4 cell count

ART = antiretroviral therapy; IQR = interquartile range; SA=South African

unstable social environment, generally more common among foreigners, may decrease ART adherence.[29–31]

Our data have several limitations. Firstly, comparison of parameters between the group with unknown (24% of cases) and known country of origin showed several differences, suggesting worse ART outcomes in patients with unknown status. In the clinic setting, and with the presence of xenophobia in the community, foreigners may be less likely to disclose their nationality. We might infer, therefore, that the group with unknown country of origin comprises predominantly foreigners, and correctly

Table 3 **Multiple logistic regression analysis of factors associated with failure of antiretroviral treatment in patients receiving treatment for more than six months**

Variable	Category	Univariate odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Self-identified citizenship status	Citizen	1.0		1.0	
	Foreigner	0.44 (0.27–0.72)	<0.001	0.45 (0.23–0.87)	0.017
	Unknown citizenship	1.6 (0.92–2.8)	0.09	1.7 (0.79–3.5)	0.18
Age category	16–29 years	1.0		–	
	30–39 years	0.89 (0.51–1.6)	0.69	–	
	>40 years	1.1 (0.59–2.0)	0.81	–	
Gender	Female	1.0		–	
	Male	1.3 (0.87–2.0)	0.19	–	
Opportunistic infections	TB before ART	2.1 (1.4–3.2)	<0.001	2.5 (1.4–4.5)	0.002
	TB after ART	2.0 (0.80–5.1)	0.13	–	
	Cryptococcosis before ART	4.9 (1.3–19.0)	0.01	–	
	Cryptococcosis after ART	2.4 (0.5–10.8)	0.25	–	
Admissions	Any admission recorded in client record	5.5 (2.8–10.8)	<0.001	–	
Site of initiation of ART	Elsewhere	1.0		–	
	At Nazareth House	0.22 (0.14–0.35)	<0.001	–	
Baseline CD4 cell count in patients initiating ART at the clinic	0–49	1.0		1.0	
	50–99	0.67 (0.33–1.4)	0.27	0.67 (0.31–1.4)	0.29
	≥100	0.82 (0.44–1.5)	0.52	0.96 (0.50–1.9)	0.91
Time period of initiation	2004	1.9 (0.95–3.8)	0.06	–	
	2005	1.1 (0.64–1.9)	0.71	–	
	2006	1.0		–	
ART initiated by	Doctor	1.0		–	
	Nurse	0.47 (0.2–1.1)	0.08	–	

ART = antiretroviral therapy; TB = tuberculosis; CI = confidence interval

assigned, this group may diminish the size of the difference between the citizen and non-citizen groups. However, it is equally possible that the unknown group may have been predominantly South African as the language and accent of foreigners are reportedly easily distinguishable from citizens. The second major limitation is that it was not possible to assess variation in treatment outcome according to the duration of settlement and degree of integration into society of foreigners. Given that the foreigners in this study comprise refugees, economic migrants and other subgroups, it is difficult to generalize these findings to refugees living in settlements or camps, for example, or to countries that do not have integrative refugee policies.

Successful management of the HIV epidemic includes access to means that would limit transmission of the virus (among which is ART), and facilitate maintenance of health of infected persons. Denying migrants access to antiretroviral treatment and other services, not only increases their social and economic burden of ill health, but also raises the risk of transmission of HIV and infectious conditions commonly seen in advanced HIV disease (especially tuberculosis).[32,33] Furthermore, HIV-related sickness may result in individuals having to stop their livelihood activities and become dependent upon others, thus hindering integrative efforts.[6] Ensuring migrants access to ART is thus beneficial not only for the migrant population but also for adoptive communities. Nazareth House HIV clinic has been able to provide ART effectively to all population groups and this approach should be applied at public health facilities across South Africa.

In conclusion, by providing evidence for a good response to ART among migrants, these findings support the recommendation of United Nations High Commissioner for Refugees[11] that ART should not be withheld from these populations. In addition, the findings presented here support the long-neglected need for full implementation of South African policies to ensure the right to access ART for all.

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