Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2005;34:979–986
doi:10.1093/ije/dyi164

COHORT PROFILES

Cohort Profile: Antiretroviral Therapy in Lower Income Countries (ART-LINC): international collaboration of treatment cohorts

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Study Group*

Dedication

This manuscript is dedicated to the memory of Dr Nicholas Hone, pioneer of HIV care in Botswana and member of the ART-LINC collaboration, who died prematurely at the beginning of the project.

How did the study come about?

Highly active antiretroviral therapy (HAART), a combination of at least three drugs, has substantially improved the prognosis of HIV-infected patients in industrialized countries.[1–3] In resource-poor settings in Africa, Asia, and South America, where 90% of people with HIV/AIDS live, access to HAART continues to be limited. It is estimated that one million HIV-1 infected individuals presently receive HAART in low-income and middle-income countries, which represents only 15% of the 6.5 million people urgently in need of such treatment in these settings.[4] International and bilateral initiatives, including WHO's '3 by 5' target (3 million patients treated by 2005), the Global Fund to fight AIDS, Tuberculosis and Malaria, and the United States President's Emergency Plan for AIDS Relief (PEPFAR), aim to substantially increase access to antiretroviral treatment in these settings during the next few months.

Clinical and epidemiological research has been conducted at the level of selected centres regarding treatment response,[5–8] programme management,[9,10] the use of generic medications,[11,12] occurrence of side effects,[13] and adherence to treatment.[14,15] However, data are still limited and the World Health Organization (WHO) and others have called for a focused operational research agenda, which will produce data on 'what works, what does not work, and why'.[16] As the 'scaling-up' of antiretroviral treatment proceeds rapidly, it is imperative that this research be timely and rooted in routine clinical management.

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration, a network of HIV/AIDS treatment programmes and cohorts in Africa, South America, and Asia was set up in 2003 to address these questions.

Who set ART-LINC up and how is it funded?

The coordinating team (see Appendix) identified potential clinical sites and cohorts treating HIV-infected patients with HAART in resource-limited settings by screening abstracts of international conferences, performing MEDLINE searches, and through personal contacts. The ART-LINC Collaboration is funded by the National Institutes of Health (Office of AIDS Research) in the United States, and the Agence Nationale de Recherches sur le Sida (ANRS) in France. Centres have recruited their cohorts and organized follow-up of patients locally. Funding to ART-LINC is devoted to coordination, training, and support in standardizing and harmonizing data collection, quality assessment and control, and data management and statistical analysis of pooled data.

What does ART-LINC cover and who is included in the sample?

The three primary objectives of ART-LINC are (i) to define the prognosis of HIV-1 infected patients treated with HAART in resource-limited settings; (ii) to compare the experience between different settings, delivery modes and types of monitoring; and (iii) to compare prognosis in resource-limited settings with that observed in industrialized nations. Importantly, both individual and programme level characteristics are of interest in this context. A similar network of HIV treatment clinics and cohorts in Europe and North America, the Antiretroviral Therapy (ART) Cohort Collaboration[1] provides data for comparative analyses of treatment outcomes in low-income and high-income settings.

A total of 31 centres in 18 low-income [gross national income per capita up to US $765 in 2003[17]] or middle-income ($766–9385) countries were contacted. To be eligible, centres needed to prospectively collect information on patients treated with HAART. At the time of writing this article 23 centres have agreed to participate and 18 centres have contributed data to the collaborative database. The current database includes patients from 13 African countries (Botswana, Burundi, Cameroon, Democratic Republic of Congo, Côte d'Ivoire, Kenya, Malawi, Morocco, Nigeria, Rwanda, Senegal, South Africa, and Uganda), Brazil, India, and Thailand (Figure 1). At all sites local ethics committees or institutional review boards had approved the collection of data.

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Figure 1 Countries with clinical centres participating in ART-LINC

Characteristics of treatment programmes

HAART was introduced in 1996 in Brazil, between 1996 and 2000 in the two Asian centres, during 1997–99 in West and North Africa, in 2001 in the Central and East African centres, and in 2000 or 2001 in most of the Southern African clinics. The characteristics of the 23 treatment programmes are summarized in Table 1. Nine centres (39%) were public, generally funded through the Ministries of Health. The remaining were either private for-profit (n = 4), or private not-for-profit programmes run by non-governmental organizations (NGOs) (n = 10). At the end of 2003 the median number of HIV-infected patients registered was 1800 per programme (range: 79–7000) and the median number of HAART-treated patients was 542 (range: 70–3000) (Table 1). Six programmes had multiple treatment sites and 15 treated children as well as adults. Levels of staffing of HIV/AIDS care programmes varied, with a median number of nine medical doctors, medical assistants or nurses per centre (range: 3–42), or a median ratio of 160 HIV-infected patients per staff member (range: 26–1167). In nine centres antiretroviral drugs were primarily supplied by government and 16 centres reported having access to generic drugs. Costs to patients varied: 12 programmes charged for drugs (median: 31 US dollars; range: 8–198 US dollars per month), 14 for CD4 + T-lymphocyte counts (CD4 counts; median: 23.5 US dollars; range: 10–33.5 US dollars per measurement) and 10 charged consultation fees (median: 6 US dollars; range: 1–44.4 US dollars per consultation). HIV-1 plasma viral load determinations were available in 17 centres but cost was high (50–100 US dollars) and testing was infrequent. Eleven centres provided free care (free drugs and no consultation fee, or a minimal one according to local standards).

The centres' eligibility criteria for initiating HAART were advanced immunodeficiency (CD4 cell count <200 cells/μl or <350 cells/μl) or advanced clinical disease according to WHO or CDC stages. Pre-treatment counselling or psycho-social preparation were part of the protocol in 18 centres. Most programmes were associated with or provided other services, including voluntary counselling and testing (18 centres), prevention of mother to child transmission (15 centres), and specialized tuberculosis clinics (13 centres). Eighteen centres had systems in place for tracing patients lost to follow-up, using telephones or home visits.

Patient characteristics

The current dataset from the ART-LINC collaboration includes a total of 8734 patients. Table 2 shows the characteristics at the start of HAART of the 7075 individuals with complete sociodemographic data, known date of starting HAART, and at least one follow-up visit, separately for treatment-naïve and treatment-experienced patients, and patients with and without baseline CD4 cell measurements. The majority of patients (n = 6498, 92%) were treatment-naïve and 73% (n = 5193) had a CD4 count at baseline. Compared with treatment-naïve patients, treatment-experienced patients were more likely to be men (65% vs 54%; $P < 0.001$), to have started HAART before 2002 (49% vs 25%; $P < 0.001$), and less likely to be treated in a public clinic (42% vs 67%; $P < 0.001$). Treatment-experienced patients had higher baseline CD4 counts at the time of HAART initiation, although both in treatment-experienced and treatment-naïve patients median baseline CD4 counts were <200 cells/mm^3. Compared with patients starting HAART without an immunological assessment, those with a documented baseline CD4 count were less likely to be male (49% vs 69%; $P < 0.001$) and more likely to be treated in publicly funded centres (75% vs 42%; $P < 0.001$) or programmes offering free care (49% vs 19%; $P < 0.001$). The proportion of patients starting HAART with a documented baseline CD4 count was lower in the most recent calendar period (2002–2003) compared with the earlier periods (71% vs 86%; $P < 0.001$).

Table 1 Characteristics of the 23 ART-LINC treatment programmes providing HAART in low-income and middle-income countries

Region	Centre code	Public clinic	Total No. of HIV + patients	Month of HAART introduction	Total No. of patients on HAART	Number of staff[a]	Number of patients per staff[a]	Use of generic drugs	Cost per month of treatment[b]	Cost per consultation[b]	Cost per CD4 + count[b]	Free care[c]	Patient tracing[c]	No. of patients in analysis
Asia	A	No	6000	06/00	1367	24	250	Yes	30.0	2.5	25.0	No	No	1365
	B	No	1000	06/96	100	25	40	Yes	None	None	10.0	Yes	Yes	92
Brazil	C	Yes	7000	01/95	3000	42	167	Yes	None	None	None	Yes	No	580
	D	Yes	1600	10/96	854	9	178	Yes	None	None	None	Yes	No	670
North and West Africa	E	No	2218	12/98	215	7	317	No	None	1.0	21.0	Yes	Yes	137
	F	No	2400	06/98	2363	8	300	No	70.8	14.0	26.0	No	Yes	–
	G	No	4500	01/97	402	11	409	Yes	10.0	None	None	No	Yes	–
	H	Yes	680	06/99	430	13	52	No	None	None	None	Yes	Yes	422
	I	Yes	1800	01/98	115	18	100	Yes	8.0	8.0	25.0	No	Yes	113
	J	Yes	5000	08/98	700	6	833	Yes	None	4.0	None	Yes	Yes	153
Central and East Africa	K	No	231	01/01	130	3	77	Yes	28.2	11.3	21.5	No	No	–
	L	Yes	600	01/01	118	9	67	Yes	None	1.0	None	Yes	Yes	115
	M	Yes	2075	11/01	909	29	72	Yes	32.0	None	22.0	No	Yes	928
	N	No	189	09/01	107	3	63	Yes	None	None	15.0	Yes	Yes	104
	O	No	3000	08/98	877	4	750	Yes	49.0	3.0	33.5	No	Yes	737
	P	NA	79	09/02	79	3	26	Yes	27.0	None	30.0	No	Yes	75
Southern	Q	No	1000	01/00	900	11	91	No	197.9	18.7	33.0	No	Yes	283
Africa	R	Yes	4000	05/00	1600	11	364	Yes	25.0	None	15.0	No	No	1503
	S	Yes	650	06/96	542	5	130	No	None	None	None	Yes	Yes	313
	T	No	4500	05/01	771	9	500	Yes	None	None	None	Yes	Yes	286
	U	No	1800	06/96	1100	6	300	No	177.8	44.4	13.3	No	Yes	–
	V	No	3500	01/01	70	3	1167	No	None	None	None	Yes	Yes	62
	W	No	800	10/97	150	5	160	Yes	32.0	None	19.0	No	Yes	–

NA, not applicable (cohort *P* was recruited in several clinical centres); HAART, highly active antiretroviral therapy.

[a] Medical doctors, medical assistants, and nurses.

[b] Costs charged to patients in US dollars.

[c] See definitions in Characteristics of treatment programmes section.

Table 2 Characteristics at the start of HAART of 7075 patients followed-up in 18 ART-LINC centres, 1996–2003

	Treatment-naïve		Treatment-experienced	
	Baseline CD4 count measured	Baseline CD4 count not measured	Baseline CD4 count measured	Baseline CD4 count not measured
	n = 4810 (100%)	n = 1688 (100%)	n = 383 (100%)	n = 194 (100%)
Age (years)				
Median (IQR)	36 (30–42)	33 (29–40)	35 (30–42)	32 (28–39)
Gender				
Male	2349 (49%)	1162 (69%)	216 (56%)	157 (81%)
Presumed HIV transmission				
Heterosexual	4719 (98%)	1682 (100%)	359 (94%)	193 (96%)
Injection drug use	91 (2%)	6 (0.4%)	24 (6%)	1 (0.5%)
Clinical stage				
Advanced[a]	1325 (28%)	153 (9%)	175 (46%)	5 (3%)
Unknown	2210 (46%)	1386 (82%)	105 (27%)	184 (95%)
CD4 count (cells/mm^3)				
Median (IQR)	108 (37–210)	–	166 (63–320)	–
<50	1474 (31%)	–	85 (22%)	–
50–199	2022 (42%)	–	130 (34%)	–
⩾200	1314 (27%)	–	168 (44%)	–
Type of HAART				
2 NRTIs + PI	900 (19%)	181 (11%)	100 (26%)	36 (19%)
2 NRTIs + NNRTI	3391 (71%)	1457 (86%)	88 (23%)	148 (76%)
Year of starting HAART				
1996–97	180 (3.7%)	26 (2%)	60 (16%)	7 (4%)
1998–2001	1204 (25%)	195 (12%)	184 (48%)	33 (17%)
2002–03	3426 (71%)	1467 (87%)	139 (36%)	154 (79%)
Type of centre and care				
Public centre	3612 (75%)	715 (42%)	212 (55%)	28 (14%)
Free care	2366 (49%)	314 (19%)	230 (60%)	8 (4%)
Availability of other laboratory data				
Total lymphocyte count	2305 (48%)	218 (13%)	150 (39%)	2 (1%)
Hæmoglobin measurement	2294 (48%)	390 (23%)	164 (43%)	17 (9%)
HIV-1 RNA plasma viral load	1801 (37%)	83 (5%)	155 (40%)	1 (0.5%)

IQR, interquartile range; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a] CDC stage C or WHO stage 4.

Treatment regimens

Table 3 summarizes the antiretroviral combinations most commonly prescribed. Overall, the most prescribed combination was stavudine (d4T), lamivudine (3TC), and nevirapine (NVP) (41%). These three drugs were given separately in 22% of all prescriptions, but clinics in the Southern Africa region mainly used the generic fixed-dose combination Triomune™. Zidovudine (ZDV), 3TC, and efavirenz (EFZ) (11%), ZDV, 3TC, and NVP (9%) and d4T, 3TC, and EFZ (6%) were also commonly used drug combinations. Altogether, the four WHO recommended first-line HAART regimens[16] accounted for 66% of all prescribed regimens. Less than 1% of patients were prescribed triple nucleoside reverse transcriptase inhibitors (NRTIs) combinations. There were variations across regions, with EFZ-based combinations more frequently used in Brazil and North and West Africa. Overall and in all regions, regimens based on a non-nucleoside reverse transcriptase inhibitor accounted for the majority of prescriptions in 2002 and 2003 (5959 patients, 89%), whereas protease inhibitor based regimens dominated in earlier years (Table 3; Figure 2).

How often are participants followed-up and what is measured?

The frequency of follow-up visits varies by cohort and by patient, depending on the clinical status of the patient, time since initiation of treatment (i.e. follow-up visits are recommended to be more frequent in the first weeks and months), and the presence of co-morbidities and adverse effects. Measurements of CD4 counts are planned every 4–6 months.

Using a standardized, field-tested site assessment tool, the characteristics of treatment programmes were recorded in late

Table 3 Antiretroviral drug combinations commonly prescribed in 18 ART-LINC centres, 1996–2003

	Overall[a]	North and West Africa	Central and East Africa	Southern Africa	Brazil	Asia
Number of centres	18	6	3	5	2	2
Number of patients	7938 (100%)	1044 (100%)	1740 (100%)	2447 (100%)	1250 (100%)	1457 (100%)
Number of patients (%)						
d4T + 3TC + NVP	1770 (22.3%)	80 (7.7%)	859 (49.4%)	15 (0.6%)	23 (1.7%)	793 (54.4%)
d4T + 3TC + NVP as Triomune™	1489 (18.8%)	0	0	1489 (60.9%)	0	0
ZDV + 3TC + EFZ	853 (10.7%)	167 (16.0%)	112 (6.4%)	185 (7.6%)	321 (25.7%)	68 (4.7%)
ZDV + 3TC + NVP	694 (8.7%)	129 (12.4%)	48 (2.8%)	130 (5.3%)	67 (5.4%)	320 (22.0%)
d4T + 3TC + EFZ	465 (5.9%)	113 (10.8%)	210 (12.1%)	14 (0.6%)	44 (3.5%)	84 (5.8%)
ZDV + 3TC + IDV	291 (3.7%)	139 (13.3%)	22 (1.3%)	3 (0.1%)	96 (7.7%)	31 (2.1%)
d4T + DDI + EFZ	207 (2.6%)	58 (5.6%)	90 (5.2%)	48 (2.0%)	6 (0.5%)	5 (0.3%)
ZDV + 3TC + NLF	159 (2.0%)	22 (2.1%)	29 (1.7%)	9 (0.4%)	99 (7.9%)	0
d4T + 3TC + IDV	150 (1.9%)	34 (3.3%)	8 (0.5%)	0	95 (7.6%)	13 (0.9%)
3TC + d4T + NLF	101 (1.3%)	10 (1.0%)	11 (0.6%)	9 (0.4%)	71 (5.7%)	0
ZDV + DDI + EFV	91 (1.1%)	82 (7.9%)	0	1 (0%)	7 (0.6%)	1 (0%)
d4T + DDI + IDV	84 (1.1%)	63 (6.0%)	8 (0.5%)	0	10 (0.8%)	3 (0.2%)
ZDV + 3TC + IDV/rtv	77 (1.0%)	3 (0.3%)	7 (0.4%)	1 (0%)	53 (4.2%)	13 (0.9%)
d4T + DDI + NVP	68 (0.9%)	1 (0%)	12 (0.7%)	4 (0.2%)	7 (0.6%)	44 (3.0%)
3 NRTIs[b]	66 (0.8%)	2 (0.2%)	6 (0.3%)	42 (1.7%)	14 (1.1%)	2 (0.1%)
d4T + DDI + NLF	66 (0.8%)	10 (1.0%)	4 (0.2%)	14 (0.6%)	35 (2.8%)	3 (0.2%)
3TC + DDI + EFV	41 (0.5%)	40 (3.8%)	1 (0%)	0	0	0
d4T + DDI + ATZ	40 (0.5%)	0	0	40 (1.6%)	0	0
ZDV + 3TC + DLV	38 (0.5%)	0	3 (0.2%)	35 (1.4%)	0	0
ZDV + DDI + IDV	33 (0.4%)	13 (1.2%)	1 (0%)	1 (0%)	18 (1.4%)	0

[a] First 20 most frequent drug combinations.
[b] Out of the following: ZDV, 3TC, DDC, d4T, DDI, and ABC.

2003 or early 2004. This includes information regarding the use of generic drugs, types of monitoring, costs to patients for drugs, consultations, and laboratory work, tracing of patients lost to follow-up, and the presence of other services and clinics. These assessments will be updated annually. Collection of information on patients includes sociodemographic data, date of start of HAART, type of treatment initiated, and, where available, CD4 counts and HIV-1 plasma RNA levels at baseline and during follow-up. The primary endpoint is mortality from all causes. Incident opportunistic infections and other clinical outcomes are also recorded, but data are less complete.

What is attrition like?

At present attrition is difficult to estimate because the duration of follow-up is limited. We examined the proportion of patients lost to follow-up among the 4810 treatment-naïve patients with complete baseline data and a least one follow-up visit (Table 2). The median duration of follow-up was 0.97 year (interquartile range: 0.41–1.93 years). Loss to follow-up was defined as the proportion of patients who were seen in the first year of therapy and who should have been, but were not, seen in the subsequent year. A total of 727 such patients (15%) were identified. The percentage lost to follow-up across clinics ranged from 3.7 to 44%. Further analysis of the patterns of early loss to treatment and their determinants is in progress.[18] In particular, it is important to clarify in what proportion of patients loss to follow-up in a given treatment centre is equivalent to stopping antiretroviral treatment, and progression to death.

What has ART-LINC found?

The descriptive analyses presented above show that only 39% of the participating clinics were publicly funded, indicating that the private health sector, profit-oriented or not, plays an important role in the delivery of HAART in lower income countries. The important contribution of NGO's raises the issue of the long-term sustainability of treatment programmes. Among the 12 centres charging patients for care, the median cost per year of treatment represented a substantial proportion of the per capita income in low-income countries.[17] The 'inverse equity hypothesis',[19] which stipulates that health inequities will get worse as effective new public health interventions initially reach those of higher socioeconomic status and only later the poor, may, therefore, be borne out in the case of HAART in resource-poor settings.[20] The baseline data also indicate important differences between patients with and without follow-up information, and with and without baseline CD4 count, in terms of the type of clinic accessed (e.g. public or private) and the sociodemographic and clinical characteristics of patients.

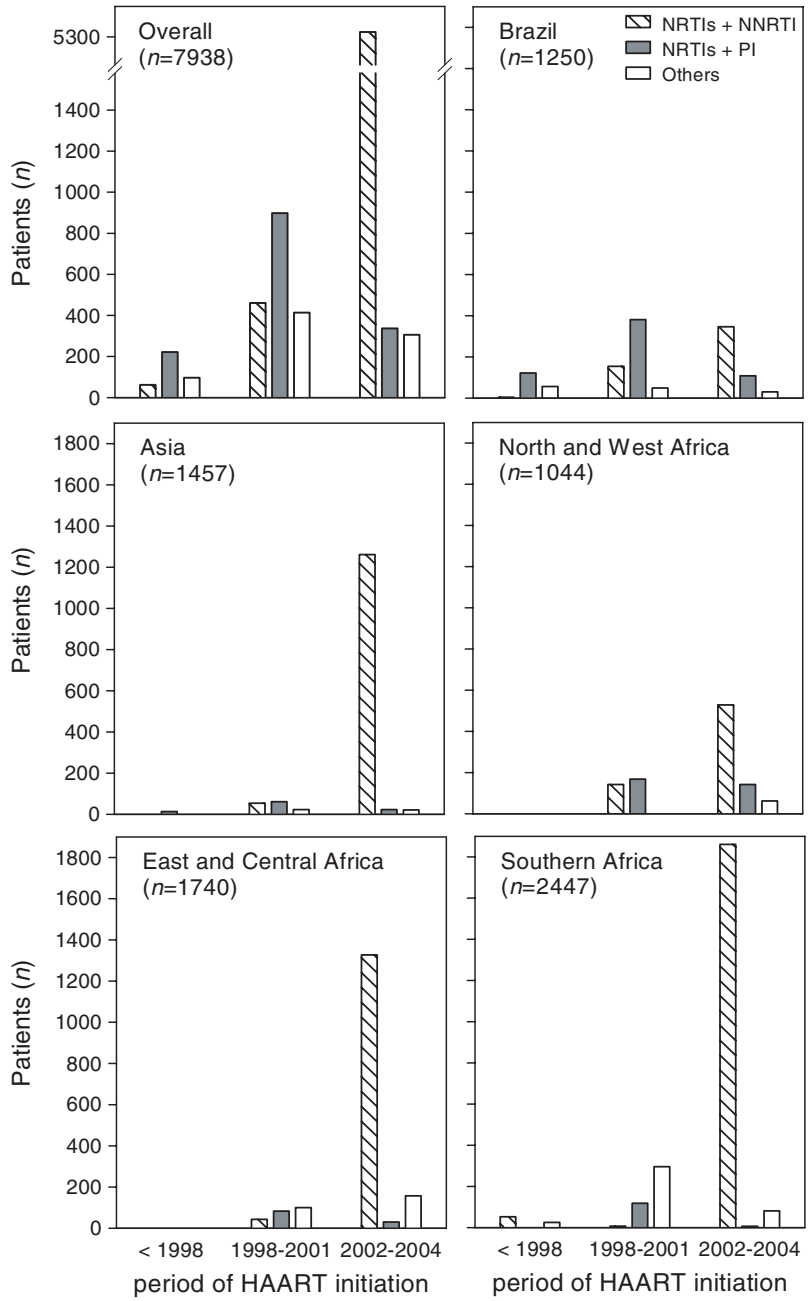

Figure 2 Distribution of type of HAART regimen used, by region and time period. ART-LINC Collaboration, 1996–2003. (HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor)

The combinations of antiretroviral drugs used generally correspond to the WHO recommendations,[16] indicating that these guidelines are useful, applicable, and, in principle, followed by public and private providers. In many centres laboratory follow-up, including CD4 count was not systematically performed. This is probably the result of technical and cost limitations rather than an attempt to simplify laboratory monitoring, an approach that requires proper evaluation.[21]

Analyses comparing survival during the first year of HAART in ART-LINC with early mortality in high-income countries (data from the ART Cohort Collaboration[1,22]) have recently been presented.[23] The analysis is based on the 4810 ART-LINC patients with complete baseline data (Table 1), and 165 deaths during 3744 person-years of follow-up. We used Weibull random effect survival models. The random effect, or shared frailty, is used to describe the unaccounted for heterogeneity between treatment programmes, which leads to the differential survival patterns.[24,25] Models included both individual level (age, sex, baseline CD4 cell count, and type of initial regimen) and programme level characteristics (free access to treatment, use of generic drugs, routine monitoring of virologic response, tuberculosis clinic on site, and intensity of efforts to trace patients).

The results will be presented in detail elsewhere. Briefly, mortality rates fell dramatically within the first few months of potent antiretroviral treatment and approached those observed in Western Europe and North America after 4–6 months of HAART. Patients in low-income settings started potent antiretroviral treatment with considerably more advanced immunodeficiency than patients from industrialized countries in Western Europe and North America. Of note, the provision of treatment free of charge to patients was associated with lower mortality in low-income settings.

Strengths and weaknesses of the ART-LINC Collaboration

The ART-LINC Collaboration is, to our knowledge, the first to describe and compare ART programmes and their adult patients in a wide range of resource-constrained settings from three continents, after a recent report describing 598 patients treated with HAART in 11 sites in Asia.[26] Important strengths include the large number of clinics and cohorts participating, with a sizeable number of patients being included in the analysis. These treatment centres and their patients represent a broad diversity of types of programmes, patients, and delivery methods. ART-LINC also examines the intersection between programme and patient characteristics, and will be able in future analyses to more fully examine the impact of programme level characteristics on patient outcomes. Finally, it demonstrates the feasibility of assembling such an international collaborative database of treatment cohorts.

The large number of patients and events is a strength however, follow-up is still limited. Also, ART-LINC is currently restricted to adult patients and results are not applicable to infants and children. The inclusion of infants and children is an important objective for future updates. Loss to follow-up might bias results if attrition is informative, i.e. associated with mortality. This has recently been demonstrated in a randomized trial in Abidjan, Côte d'Ivoire.[27] We will examine this issue in detail and consider analyses of a combined endpoint of death or lost to follow-up. CD4 cell counts were available only in selected patients who may differ in important respects, for example in their adherence to therapy or access to care. ART-LINC data on causes of death, co-morbidities, and access to prophylaxis and treatment for opportunistic infections are also incomplete at present.

ART-LINC is an ongoing initiative, which will continue to monitor outcomes in HIV-1-infected patients on HAART in low-income settings, and update analyses at regular intervals. The improvement and harmonization of the collection of baseline and follow-up data is an important goal for the next update of the collaborative database.

Can I get hold of the data? Where can I find out more?

Collaborators sign an agreement to allow their data to be used in ART-LINC, however, the data remain the property of the participating centres and all analyses have to be approved by the Steering Group (see Appendix). Eligible treatment programmes can gain access to the data by joining ART-LINC. Readers who wish to find out more should visit the ART-LINC website at www.art-linc.org.

Acknowledgements

The ART-LINC Collaboration wishes to gratefully acknowledge the funders of the project, the National Institutes of Health (Office of AIDS Research) in the United States, and the Agence Nationale de Recherches sur le Sida (ANRS) in France. Special thanks to Jack Whitescarver, Michel Kazatchkine, and Brigitte Bazin for their continuous encouragement and support. The authors also wish to thank all the patients and collaborating centre staff, who made this project possible. We are grateful to the support staff of the Institute of Social and Preventive Medicine at the University of Bern (Switzerland) and the Institut de Sante Publique et Developpement at the University Victor Segalen Bordeaux 2 (France), especially to Marie-Pierre Martin, Malcom Sturdy, and Lotti Senn. Special thanks to Besigin Tonwe-Gold (Abidjan) and Jessica Oyugi (Kampala) for their assistance in the field.

References

[1] Egger M, May M, Chene G *et al*. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;**360:**119–29.

[2] Hogg RS, Yip B, Kully C *et al*. Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *CMAJ* 1999;**160:**659–65.

[3] Mocroft A, Vella S, Benfield TL *et al*. Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998;**352:** 1725–30.

[4] World Health Organization. Progress on Global Access to HIV Antiretroviral Therapy. An update on '3 by 5'. June 2005. Geneva: World Health Organization, 2005.

[5] Weidle PJ, Malamba S, Mwebaze R *et al*. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet* 2002;**360:**34–40.

[6] Marins JR, Jamal LF, Chen SY *et al*. Dramatic improvement in survival among adult Brazilian AIDS patients. *AIDS* 2003;**17:**1675–82.

[7] Seyler C, Anglaret X, Dakoury-Dogbo N *et al*. Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Cote d'Ivoire. *Antivir Ther* 2003;**8:**385–93.

[8] Coetzee D, Hildebrand K, Boulle A *et al*. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;**18:**887–95.

[9] Farmer P, Leandre F, Mukherjee J, Gupta R, Tarter L, Kim JY. Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bull World Health Organ* 2001;**79:**1145–51.

[10] Desclaux A, Ciss M, Taverne B *et al*. Access to antiretroviral drugs and AIDS management in Senegal. *AIDS* 2005;**17(Suppl. 17):** S95–S101.

[11] Kumarasamy N, Solomon S, Chaguturu SK *et al*. The safety, tolerability and effectiveness of generic antiretroviral drug regimens for HIV-infected patients in south India. *AIDS* 2003;**17:**2267–69.

[12] Bourgeois A, Laurent C, Mougnutou R *et al*. Field assessment of generic antiretroviral drugs: a prospective cohort study in Cameroon. *Antivir Ther* 2005;**10:**335–41.

[13] Law WP, Dore GJ, Duncombe CJ *et al*. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996–2001. *AIDS* 2003;**17:**2191–99.

[14] Laniece I, Ciss M, Desclaux A *et al*. Adherence to HAART and its principal determinants in a cohort of Senegalese adults. *AIDS* 2003;**17 (Suppl. 3):**S103–S108.

[15] Oyugi JH, Byakika-Tusiime J, Charlebois ED *et al*. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *J Acquir Immune Defic Syndr* 2004;**36:**1100–02.

[16] WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach*. Geneva: World Health Organisation, 2003.

[17] The World Bank Group. Country classification. http://www.worldbank.org/data/countryclass/countryclass.html. (Accessed July 2005).

[18] Balestre E, Brinkhof M, Dabis F *et al*. Short-term incidence and risk factors for being lost to treatment in 16 antiretroviral treatment cohorts in low income countries. In: Proceedings of the Third Annual International AIDS Society Conference on HIV Pathogenesis and Treatment, Abstract MoPe11.10C13. 24–27 July 2005, Rio de Janeiro, Brazil.

[19] Victora CG, Vaughan JP, Barros FC, Silva AC, Tomasi E. Explaining trends in inequities: evidence from Brazilian child health studies. *Lancet* 2000;**356:**1093–98.

[20] Egger M, Boulle A, Schechter M, Miotti P. Antiretroviral therapy in resource-poor settings: scaling up inequalities? *Int J Epidemiol* 2005;**34:**509–12.

[21] Calmy A, Klement E, Teck R, Berman D, Pecoul B, Ferradini L. Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling-up. *AIDS* 2004;**18:** 2353–60.

[22] Chene G, Sterne JA, May M *et al*. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet* 2003;**362:**679–86.

[23] Dabis, F., Schechter, M., Egger, M., ART-LINC/ART-CC Study Groups. Response to highly active retroviral therapy in low- and high-income countries: Analysis of clinical databases from 4 continents. In: Proceedings of the 12th Conference on Retroviruses and Opportunistic Infections, Abstract 23. 22–25 February 2005, Boston, MA.

[24] Keiding N, Andersen PK, Klein JP. The role of frailty models and accelerated failure time models in describing heterogeneity due to omitted covariates. *Stat Med* 1997;**16:**215–24.

[25] Gutierrez RG. Parametric frailty and shared frailty survival models. *Stata J* 2002;**2:**22–44.

[26] Zhou J, Kumarasamy N, Ditangco R *et al*. The TREAT Asia HIV Observational Database: baseline and retrospective data. *J Acquir Immune Defic Syndr* 2005;**38:**174–79.

[27] Anglaret X, Toure S, Gourvellec G *et al*. Impact of vital status investigation procedures on estimates of survival in cohorts of HIV-infected patients from Sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2004;**35:**320–23.

Appendix

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