CCASAnet Caribbean, Central and South America network

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Failure of Initial HAART in the Caribbean, Central, and South America

Carina Cesar[1], Bryan E. Shepherd[2], Cathy A. Jenkins[2], Beatriz Grinsztejn[3], Marcelo Wolff[4], Jean W. Pape[5], Denis Padgett[6], Juan Sierra Madero[7], Eduardo Gotuzzo[8], Pedro E. Cahn[1], for CCASAnet

[1]Fundación Huésped (FH), Investigaciones Clínicas, Buenos Aires, ARGENTINA; [2]Vanderbilt University, Department of Biostatistics, Nashville, TN, USA; [3]Instituto de Pesquisa Clinica Evandro Chagas, Fundação Oswaldo Cruz (IPEC-Fiocruz), Rio de Janeiro, BRAZIL; [4]Fundación Arriarán, Universidad de Chile, Santiago, CHILE; [5]Les Centres GHESKIO, Port-au-Prince, HAITI; [6]Instituto Hondureño de Seguridad Social and Universidad Autónoma de Honduras (IHSS/HE), Tegucigalpa, HONDURAS; [7]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), Mexico City, MEXICO; [8]Instituto de Medicina Tropical Alexander von Humboldt (IMTAvH), Universidad Peruana Cayetano Heredia, Lima, PERU.

BACKGROUND

Access to highly active antiretroviral therapy (HAART) is expanding in Latin America (LAC). The aim of this study was to identify rates of failure of initial HAART and associated factors.

METHODS

Inclusion: Antiretroviral-naïve adults who started their first HAART on or after January 1, 2000 at participating CCASAnet sites (Argentina, Brazil, Haiti, Honduras, Mexico, and Peru). **Outcomes**: Time from HAART initiation until virologic failure, major regimen modification, and a composite endpoint of the first of virologic failure or major regimen modification.

Virologic failure was defined as one of the following:

1) HIV-1 viral load (VL) >400 copies >180 days after HAART initiation;
2) Undetectable VL followed by 2 subsequent VL > 400;
3) Undetectable VL followed by 1 VL > 1000.

Viral load measurements were not available for patients from the site in Haiti, so the site was not included in the virologic failure and composite endpoint analyses. Across the 5 LAC sites, median frequency of VL measurements was 3.1/year; 26% of patients from Honduras were missing VL; this proportion was less than 2% for the other sites. Major regimen change was defined as switching to a boosted protease inhibitor (PI), unless the first regimen was a boosted PI in which case a major regimen change was defined as switching the backbone PI.

Statistical Analysis: Cumulative incidence of virologic failure and major regimen change were estimated considering death as a competing event. Hazard ratios (HR) were computed using multivariable Cox models stratified by site. Analyses of predictors of major regimen change in Haiti did not include VL or probable route of infection.

Sensitivity Analyses: Patients with >1 year gap between VL measurements were censored in virologic failure and composite analyses at the date of the last measurement. Analyses were repeated using a stricter definition for virologic failure: one VL > 1000 not considered as failure.

RESULTS

The baseline characteristics of12,879 HAART initiators who met inclusion criteria are shown in **Table 1**.

Table 1. Patient characteristics at ART initiation by site

	N	FH Argentina	IPEC-Fiocruz Brazil	GHESKIO Haiti	IHSS/HE Honduras	INCMNSZ Mexico	IMTAvH Peru	Combined
		N=867	N=1817	N=6468	N=917	N=811	N=1999	N=12879
Sex	12879							
Male		71% (618)	68% (1244)	44% (2851)	54% (499)	89% (720)	71% (1413)	57% (7345)
Age of first HAART	12879	32 38 46	30 37 44	32 38 46	30 36 43	28 34 41	28 34 42	30 37 45
Probable route of infection	12879							
Heterosexual		28% (241)	51% (924)	0% (0)	61% (557)	29% (238)	66% (1311)	25% (3271)
MSM		15% (127)	34% (617)	0% (0)	6% (54)	66% (532)	34% (685)	16% (2015)
IDU		2% (16)	1% (13)	0% (0)	0% (1)	1% (10)	0% (0)	0% (40)
Other		1% (7)	1% (15)	0% (0)	0% (3)	1% (8)	0% (0)	0% (33)
Unknown		55% (476)	14% (248)	100% (6468)	33% (302)	3% (23)	0% (3)	58% (7520)
AIDS at first HAART	10221							
Not AIDS		92% (672)	49% (895)	69% (3363)	60% (418)	42% (317)	60% (792)	63% (6457)
AIDS		8% (58)	51% (921)	31% (1530)	40% (284)	58% (441)	40% (530)	37% (3764)
Baseline CD4 (cells/mm^3)	11625	114 208 279	79 210 306	63 154 240	55 115 195	48 142 260	44 110 228	60 153 251
Baseline viral load ($\log_{10}$)	4324	4.1 4.7 5.2	4.3 4.9 5.4		4.4 5.0 5.0	4.7 4.9 5.0	4.7 5.2 5.5	4.4 4.9 5.4
Initial HAART	12879							
NNRTI		77% (671)	71% (1294)	96% (6205)	95% (874)	76% (616)	95% (1902)	90% (11562)
BOOSTED PI		16% (141)	20% (365)	3% (190)	2% (18)	20% (164)	4% (88)	8% (966)
PI		3% (25)	6% (118)	0% (9)	3% (23)	2% (16)	0% (5)	2% (196)
3 NRTI		3% (28)	0% (4)	1% (64)	0% (2)	1% (7)	0% (2)	1% (107)
Other		0% (2)	2% (36)	0% (0)	0% (0)	1% (8)	0% (2)	0% (48)
Follow-up, years	12879	1.8 4.0 6.8	1.8 3.8 5.9	2.0 3.6 5.5	1.2 4.0 7.0	2.2 4.5 7.2	1.2 3.0 5.5	1.8 3.6 5.8

a b c represent the lower quartile (a), the median quartile (b), and the upper quartile (c) for continuous variables.
Numbers after percentages are counts.

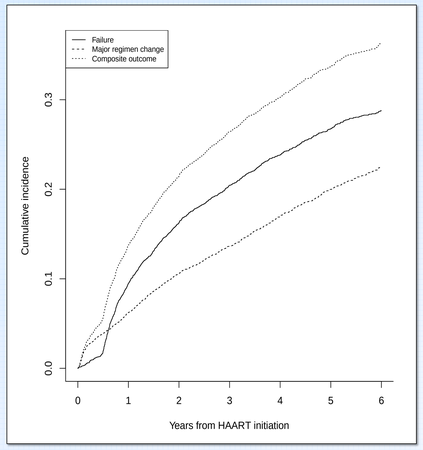
After HAART initiation among the 5 LAC sites, the following are the **cumulative incidences** at 1, 3, and 5 years, respectively:

- Virologic failure: 8.9%, 20.2%, and 26.6%.
- Major regimen change: 5.9%, 13.5%, and 19.8%.
- Composite outcome: 13.0%, 26.2%, and 33.5%.

Results were similar after censoring patients with gaps of a year or more in VL measurements. The cumulative **incidences of major regimen change were lower in Haiti** than in the 5 LAC sites: 1.2%, 5.2%, and 11.4%.

Table 2 reports the association between patient characteristics at HAART initiation and each of the 3 outcomes combined across the 5 Latin American sites. **Predictors of virologic failure** included younger age, prior AIDS, HAART start in earlier calendar years, and starting a non-NNRTI-based regimen. **Predictors of major regimen change** were similarly younger age and AIDS.

Figure 1. Cumulative incidence of virologic failure, major regimen change, and first of virologic failure or major regimen change among 5 Latin American sites (Haiti excluded).



In contrast, earlier year of first HAART was associated with a decreased risk of regimen change. Female sex was also associated with a higher risk of a major regimen change.

In a separate analysis with Haiti alone (data not shown), female sex, younger age, AIDS at first HAART, more recent calendar year at initiation, and lower CD4 were associated with a greater risk of a major regimen change. Sensitivity analyses using a stricter definition for virologic failure or censoring patients with gaps between viral load measurements delivered similar results.

Table 2. Association between patient characteristics at HAART initiation and virologic failure, major regimen change, and the first of virologic failure or major regimen change among 5 Latin American sites (Haiti excluded). Hazard ratios (HR) and 95% confidence intervals (CI) are adjusted for all other variables in the table and stratified by site.

	Failure			Major regimen change			Composite outcome		
Covariate	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Male	0.93	(0.82, 1.06)	0.29	0.72	(0.63, 0.83)	0.001	0.86	(0.77, 0.97)	0.010
Age (years)			0.001			0.001			0.001
20	1.90	(1.55, 2.33)		1.83	(1.44, 2.31)		1.75	(1.46, 2.10)	
30	1.19	(1.05, 1.34)		1.19	(1.04, 1.37)		1.17	(1.06, 1.30)	
40 (ref)	1.00			1.00			1.00		
50	0.86	(0.78, 0.94)		0.89	(0.81, 0.99)		0.90	(0.83, 0.97)	
AIDS at first HAART	1.37	(1.20, 1.57)	0.001	1.50	(1.28, 1.74)	0.001	1.30	(1.15, 1.47)	0.001
Year of first HAART			0.001			0.001			0.001
2002	1.47	(1.29, 1.68)		0.91	(0.77, 1.07)		1.25	(1.10, 1.41)	
2004	1.17	(1.11, 1.23)		0.95	(0.89, 1.01)		1.08	(1.03, 1.13)	
2006 (ref)	1.00			1.00			1.00		
2008	0.97	(0.87, 1.09)		1.08	(0.95, 1.23)		1.04	(0.94, 1.15)	
2010	1.00	(0.86, 1.16)		1.30	(1.09, 1.55)		1.17	(1.02, 1.33)	
First HAART type			0.001			0.001			0.001
NNRTI (ref)	1.00			1.00			1.00		
PI	1.29	(1.10, 1.50)		0.98	(0.82, 1.17)		1.30	(1.14, 1.49)	
Other	1.38	(1.12, 1.70)		0.51	(0.37, 0.69)		1.12	(0.92, 1.36)	
CD4 at first HAART			0.59			0.08			0.73
50	0.97	(0.82, 1.15)		1.27	(1.04, 1.55)		1.00	(0.85, 1.19)	
100	0.99	(0.84, 1.16)		1.22	(1.01, 1.46)		1.01	(0.87, 1.18)	
200	0.97	(0.88, 1.06)		1.10	(0.99, 1.23)		0.98	(0.91, 1.06)	
350 (ref)	1.00			1.00			1.00		
HIV1-RNA at first HAART ($\log_{10}$)			0.47			0.62			0.71
4	0.99	(0.86, 1.14)		0.97	(0.84, 1.11)		1.05	(0.93, 1.17)	
5 (ref)	1.00			1.00			1.00		
6	1.15	(0.97, 1.37)		0.93	(0.77, 1.13)		1.07	(0.92, 1.24)	
Probable route of infection			0.001			0.10			0.001
Heterosexual (ref)	1.00			1.00			1.00		
MSM	0.75	(0.65, 0.87)		0.84	(0.72, 0.99)		0.77	(0.68, 0.87)	
IDU	1.59	(0.97, 2.60)		1.16	(0.64, 2.13)		1.34	(0.83, 2.16)	
Other	0.88	(0.75, 1.04)		0.85	(0.70, 1.03)		0.86	(0.74, 1.00)	

CONCLUSIONS

This is the first study to evaluate rates of virologic failure and major regimen change after first HAART throughout Latin America. Rates were moderate/high, but **similar to rates reported in North America and Europe**. Trends over time may reflect availability of second line drugs. **Failure was more likely among younger patients**, suggesting the need to design specific strategies for these patients.

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