P 164

Rapid Disease Progression in HIV-1 Subtype C Infected South African Women

Nigel Garrett[1], Lise Werner[1], Koleka Mlisana[1,2,3], Lyle McKinnon[1], Francois van Loggerenberg[4], Thumbi Ndung'u[5], Clive Gray[6], Lynn Morris[1,7], Carolyn Williamson[1,3,6], Salim Abdool Karim[1,8] and the CAPRISA 002 Acute Infection Study Team

1. Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa; 2.Department of Medical Microbiology, University of KwaZulu-Natal; South Africa; 3.National Health Laboratory Services, South Africa; 4. The Global Health Network, Centre for Tropical Medicine, University of Oxford, UK;
5. HIV Pathogenesis Programme, University of KwaZulu-Natal, Durban, South Africa; 6. Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa;
7. AIDS Virus Research Unit, National Institute for Communicable Diseases, Johannesburg, South Africa; 8. Columbia University, New York City, US

Background

- HIV-1 disease progression to AIDS has been estimated as approximately 8 - 10 years in HIV clade B infected cohorts.
- Limited data on disease progression exist from African settings.
- An accurate description of the disease progression spectrum has important policy implications for the provision of antiretroviral therapy (ART).

Objectives

- To investigate risk factors for rapid HIV disease progression in a cohort of women followed from acute clade C infection.
- To estimate proportions of women requiring ART at CD4 count thresholds of <350 or <500 cells/µl.

Methods

- 839 HIV-uninfected women from seroincidence cohorts at two sites in KwaZulu-Natal were assessed for acute HIV infection monthly (n=245) or 3 monthly (n=594) for up to 4 years.
- Women diagnosed with acute infection by HIV antibody and PCR tests were followed prospectively in the CAPRISA 002 Acute Infection Study from 2004.
- Rapid disease progression was defined as reaching CD4 count <350 cells/µl by 2 years post-infection.
- Serial clinical and laboratory assessments were compared using survival analysis and logistic regression.

Results

Study Population

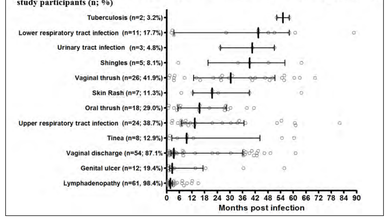
- 62 women were identified at median 42 days post-infection contributing 282 years of follow-up.
- Cohort characteristics (Table 1).
- First episode of clinical diagnoses in follow-up are shown (Figure 3).

Table 1: Demographic and behavioural characteristics of the acute HIV infection cohort

Characteristic	All (N=62)	Rapid progressors (N=27)	Non-rapid progressors (N=35)	p-value
Median days post infection at enrolment (IQR)*	42 (34 – 59)	42 (30 – 59)	46 (34 – 60)	0.804
Median Age in years (IQR)	25 (21 – 33)	27 (23 – 36)	24 (21 – 33)	0.163
Urban % (n)	74.2% (46)	85.2% (23)	65.7% (23)	0.142
Completed high school % (n)	29.0% (18)	29.6% (8)	28.6% (10)	1.000
Marital status % (n)				
Married or stable partner	71.0% (44)	59.3% (16)	80.0% (28)	0.240
Many partners	16.1% (10)	22.2% (6)	11.4% (4)	
No partners	12.9% (8)	18.5% (5)	8.6% (3)	
Number of sexual partners in last 3 months (enrolment)* % (n)				
0 to 1	68.3% (41)	55.6% (15)	78.8% (26)	0.093
2 or more	31.7% (19)	44.4% (12)	21.2% (7)	
Commercial sex workers % (n)	32.3% (20)	33.3% (9)	31.4% (11)	1.000
Condom used at last sex act % (n)	56.5% (35)	59.3% (16)	54.3% (19)	0.798
Ever had anal sex % (n)	14.5% (9)	22.2% (6)	8.6% (3)	0.160
History of tuberculosis % (n)	8.1% (5)	3.7% (1)	11.4% (4)	0.376
Median BMI at enrolment (IQR)	26.6 (23.5 – 31.8)	26.8 (23.9 – 32.1)	26.4 (22.7 – 31.3)	0.287
Mean CD4 count at enrolment (SE)	520 (193.61)	413 (128.95)	603 (195.88)	<0.001
Mean log viral load at enrolment (SE)	4.62 (0.92)	4.96 (0.84)	4.36 (0.90)	0.009
Bacterial vaginosis at enrolment % (n)	73.3% (44/60)	66.7% (18/27)	78.8% (26/33)	0.382
Any STI† at enrolment % (n)	44.3% (27/61)	40.7% (11/27)	47.1% (16/34)	0.796
HSV-2 Ab positive at enrolment % (n)	91.9% (57)	92.6% (25)	91.4% (32)	1.000
HBcAb positive at enrolment % (n)	50.0% (31)	59.3% (16)	42.9% (15)	0.306

* Enrolment defined as first HIV+ visit
† Any sexually transmitted disease defined as testing positive for *T. pallidum, T. vaginalis, N. gonorrhoeae, C. trachomatis, M. genitalium,* or HSV-2 PCR

Figure 3: Time to first episode of clinical conditions from acute HIV infection experienced by study participants (n; %)



Time to CD4<350

- 44% experienced a CD4 decline to <350 by 2 years post-infection (Figure 1).
- 79% reached CD4 <500 by 2 years.
- Progression stratified by 3 and 6-month viral load (VL) is summarized (Figure 2).

Figure 1: Superimposed Kaplan-Meier graphs of time to CD4 count <350 cells/µl and time to CD4 < 600 cells/µl since estimated date of infection

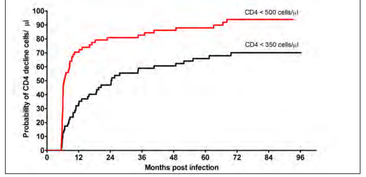
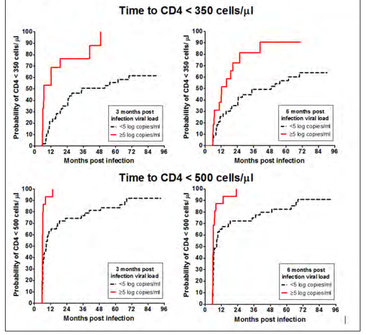


Figure 2: Kaplan-Meier graphs depicting time to CD4<350 cells/µl and CD4<500 cells/µl stratified by viral load at 3 and 6 months post infection



Predictors of Disease Progression

- Predictors of rapid progression were CD4 at 3 months post-infection, VL set-point and hepatitis B co-infection.
- Presence of any of HLA- B*1302, B*27, B*57, B*5801 or B*8101 alleles predicted non-rapid progression.

Table 2: Predictors of rapid disease progression defined as CD4 count <350 cells/µl within 2 years of infection

Variable	Level	# rapid/ # total	Unadjusted analysis Hazard ratio (95%CI)	p-value	Adjusted analysis Hazard ratio (95%CI)	p-value
Demographic and Behavioural Characteristics						
Age (per 5 year increase)			1.03 (0.85 - 1.24)	0.761	0.82 (0.55 - 1.21)	0.317
Completed high school	No	19/44	1.0 (ref)			
	Yes	8/18	1.09 (0.48 - 2.49)	0.840		
Marital status	Married or stable partner	16/44	1.0 (ref)		1.0 (ref)	
	Many partners	6/10	2.05 (0.80 - 5.25)	0.135	0.19 (0.03 -1.42)	0.105
	No partner	5/8	3.03 (1.07 - 8.53)	0.036	0.22 (0.03 -1.64)	0.139
Site	Rural	4/16	1.0 (ref)		1.0 (ref)	
	Urban	23/46	2.47 (0.85 - 7.14)	0.096	2.09 (0.41- 10.63)	0.374
Number of sexual partners in last 3 months	0 to 1	15/41	1.0 (ref)		1.0 (ref)	
	2 or more	12/19	2.06 (0.96 - 4.41)	0.063	4.21 (0.70-25.35)	0.117
Condom at last sex act	Yes	16/35	1.0 (ref)			
	No	11/27	0.84 (0.39 - 1.82)	0.666		
Sex worker	No	18/42	1.0 (ref)			
	Yes	9/20	1.07 (0.48 - 2.39)	0.864		
Ever had anal sex	No	21/53	1.0 (ref)		1.0 (ref)	
	Yes	6/9	1.93 (0.78 - 4.79)	0.157	0.91 (0.23 - 3.57)	0.894
Routine Clinical and Laboratory Assessment						
Personal or family history of hypertension or diabetes	No	15/34	1.0 (ref)			
	Yes	12/28	0.93 (0.44 - 1.99)	0.858		
Creatinine count at 3 months (mo.) post infection			0.96 (0.91 - 1.01)	0.087	0.97 (0.91 - 1.04)	0.369
History of tuberculosis	No	26/57	1.0 (ref)			
	Yes	1/5	0.40 (0.05 - 2.97)	0.373		
BMI at enrolment (kg/m²)			0.99 (0.94 - 1.05)	0.823		
Haemoglobin at 3 mo. (g/dL)	≥12	15/31	1.0 (ref)			
	<12	12/31	0.72 (0.33 - 1.53)	0.387		
Neutrophil count at 3mo. ($x10^9/l$)	≥2.5	13/29	1.0 (ref)			
	<2.5	14/32	1.03 (0.49 - 2.20)	0.932		
Platelets at 3 mo. ($x10^9/l$)			1.00 (0.99 - 1.00)	0.692		
Elevated liver function tests at 3 mo.**	No	22/51	1.0 (ref)			
	Yes	5/11	1.00 (0.38 - 2.65)	0.993		
CD4+ count decline from baseline (by 10% decrease)			1.56 (1.12 - 2.17)	0.008		
CD4+ count at 3 mo. (by 100 cells/µl decrease)			1.98 (1.43 - 2.74)	<0.001	2.07 (1.31 - 3.28)	0.002
Log viral load at 3 mo. (by 1 log increase)			2.77 (1.63 - 4.70)	<0.001	3.82 (1.51 - 9.67)	0.005
Any STI at enrolment	No	16/34	1.0 (ref)			
	Yes	11/27	0.58 (0.38 - 1.78)	0.621		
Hepatitis-B core Ab status at enrolment	Negative	11/31	1.0 (ref)		1.0 (ref)	
	Positive	16/31	1.52 (0.70 - 3.27)	0.287	4.54 (1.31 - 15.69)	0.017
Hepatitis-B Ab status at 6 mo.	Remained negative	7/24	1.0 (ref)			
	Baseline positive	14/27	2.10 (0.85 - 5.22)	0.109		
	New infection	3/3	8.98 (2.21 - 36.47)	0.002		
HLA types						
Protective HLA-B types#	No	24/47	1.0 (ref)		1.0 (ref)	
	Yes	3/15	0.30 (0.09 - 0.99)	0.048	0.19 (0.05 - 0.74)	0.016
Harmful HLA-B types#	No	18/43	1.0 (ref)			
	Yes	9/19	1.04 (0.47 - 2.32)	0.922		

† Any sexually transmitted disease defined as testing positive for *T. pallidum, T. vaginalis, N. gonorrhoeae, C. trachomatis, M. genitalium,* or HSV-2 PCR.
* Due to missing data, the adjusted analysis was performed on a total of 55 participants, with 26 events of rapid disease progression.
** Elevated liver function tests defined as having ALT >35 and/or AST >35.
# Protective HLA-B types are B*1302, B*27, B*57, B*5801, B*8101. Harmful HLA-B types are B*1801, B*35, B5802.

Discussion

- Rapid HIV disease progression is common among clade C infected women from KwaZulu-Natal, South Africa, and can be predicted in early infection.
- Almost half the cohort progressed to CD4 <350 cells/µl within 2 years of infection.
- Based on this study, the majority of women would qualify for ART within the first year of infection, if the CD4 threshold was increased to 500 cells/µl in South Africa, as recommended by WHO guidelines in 2013.
- Given the high HIV incidence in KwaZulu-Natal, the dual benefit of earlier ART to reduce transmission and improve individual health in a setting where rapid progression is common, provides a strong argument for achieving greater ART coverage.

Acknowledgments

We thank all the Acute Infection Study participants who are making an important personal contribution to HIV research through their continued support and participation in our work. The scientific and supportive role of the whole CAPRISA 002 study and protocol team is gratefully acknowledged.

Contact: garrett@ukzn.ac.za

This research has been supported by the National Institute of Allergy and infectious Disease (NIAID), National Institutes of Health (NIH) (grant# AI51794), the South African National Research Foundation (grant # 67385), the Columbia University-Southern African Fogarty AIDS International Training and Research Programme (AITRP) funded by the Fogarty International Center, NIH (grant # D43TW00231) and a training grant from LifeLab, a biotechnology centre of the South African Government Department of Science and Technology.