Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second line antiretroviral regimens in resource-limited settings.

Supplementary Results 1.

Synthesis model of progression of HIV and the effect of ART (V4a). Model fit. April 2009

The following provides some further details of the comparisons of the fit to observed data of the original model of HIV progression and the effect of ART. This original model was used to provide the part of the model relating to prognosis and the effect of ART.

Table 1. Incubation period to CD4 200, AIDS and death from seroconversion (no ART)

Year from s/c	% with AIDS Observed[1]	model	% died observed[1]	model	% CD4 < 200 observed[2]	model
1	0.6	**0.1**	0.3	**0.4**		
2	2.0	**0.8**	1.4	**1.1**		
3	4.3	**2.9**	3.1	**2.3**		
4	8.1	**6.8**	5.8	**4.8**		
5	13.4	**12.1**	9.8	**8.8**		
6	19.8	**18.4**	14.8	**13.9**	25	**35.2**
7	25.9	**25.8**	20.5	**20.8**		
8	32.3	**33.6**	27.0	**28.3**	50	**52.9**
9	38.8	**41.3**	33.8	**35.8**		
10	46.1	**48.0**	40.5	**43.1**		
11	53.0	**54.1**	48.3	**49.5**		
12	58.1	**58.8**	55.4	**55.2**	75	**73.1**
13	63.0	**62.9**	62.4	**60.1**		

Table 2. Viral load set point and initial CD4 count (after primary infection)

	Observed[3]	Model
Median VL set point:	4.5	**4.0**
Median CD4:	570	**681**

Table 3. Incubation period AIDS to death (pre-ART era)

Years from AIDS diagnosis	% died observed[4]	model
1	40%	**45%**
3	84%	**76%**
median	17 mths	**15 mths**

Table 4. Association between viral load measured close to seroconversion (between 6-24 months) and risk of AIDS, adjusting for CD4 count and age. Observed data from ref 5.

	Adjusted Relative Hazard	
	Observed (95% confidence interval)	**Model**
Viral load (Per 0.5 log higher)	1.87 (1.58 – 2.20)	**1.76**
CD4 count (Per 100 cells/mm^3 higher)	1.12 (1.02 – 1.24)	**1.08**
Age (Per 10 years older)	1.19 (0.96 – 1.47)	**1.15**

Table 5. Risk of AIDS by CD4 count and viral load and age over 6 years (pre-HAART)

		Observed[6]	**Model**
CD4 < 350			
Viral load	≤ 1500 - (low n)		
	1501- 7000	19	**52**
	7001- 20000	42	**72**
	20001- 55000	73	**83**
	> 55000	92	**93**
CD4 350-500			
Viral load	≤ 1500 - (low n)		
	1501- 7000	22	**23**
	7001- 20000	40	**50**
	20001- 55000	57	**70**
	> 55000	78	**86**
CD4 > 500			
Viral load	≤ 1500 - (low n)	5	
	1501- 7000	15	**8**
	7001- 20000	26	**16**
	20001- 55000	48	**38**
	> 55000	67	**69**

***** Viral load values used in MACS may need to be multiplied by ~ 2 to approximate to more commonly used Roche assay levels.

Table 6. Median CD4 count at diagnosis of AIDS and at death (pre-HAART era)

	AIDS	death
Observed[7]:	~ 40	~ 0
Model:	**35 IQR 10 - 90**	**4 IQR 0 - 26**

Table 7. 3 year percent risk of AIDS after start of ART by baseline CD4 / viral load (age < 50, non-IDU, AIDS-free)

		Observed[8]	**Model**
Baseline viral load < 100,000			
Baseline CD4 count	< 50	16	**14**
	50 - 99	12	**13**
	100 - 199	9	**8**
	200- 349	5	**5**
	≥ 350	3	**8**
Baseline viral load ≥ 100,000			
Baseline CD4 count	< 50	20	**20**
	50 - 99	16	**16**
	100 - 199	12	**10**
	200- 349	6	**8**
	≥ 350	4	**2**

Table 8. Effect of HAART vs no therapy on risk of AIDS and death

Simulated trial with 5 years follow up
Relative hazard of AIDS
(HAART vs no therapy)

Observed[9]	model
0.10	**0.11**

Table 9. % with virologic failure (viral load > 500 copies/mL / on ART) by time from start of HAART (patients starting with PI/r or NNRTI regimen). Observed data from ref 10.

Years from start of HAART													
1		2		3		4		5		6		7	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
7%	**8%**	14%	**15%**	18%	**20%**	21%	**23%**	23%	**25%**	26%	**28%**	27%	**29%**

*****Observed data may be overestimates due to some unrecognised stopping of ART

Table 10. Rate of viral rebound in people on 1st line HAART and with viral load < 50 copies/mL

	Rate per person year
Observed[11]:	3-6
Model:	**5.8**

Table 11. Median CD4 count change at 3 years from start of HAART

Observed[12]:	273
Model:	**270**

Table 12. Viral load response to second line HAART

% with virologic failure (viral load > 500 copies/mL and on ART)

Years from start of second line HAART (modelled includes those with nucs before HAART)

Observed data from CHIC (unpublished)

1		2		3		4		5	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
32%	**32%**	42%	**46%**	49%	**51%**	56%	**56%**	59%	**59%**

Table 13. Discontinuation of drugs in initial HAART regimen

Time from start of ART to discontinuation of at least one drug in initial regimen (discontinuation for any reason)

Years from start of HAART (observed data from ref 13. - modelled data for 1996-2001 inclusive)

1		2		3		4	
obs	mod	obs	mod	obs	mod	obs	mod
30%	**32%**	45%	**47%**	62%	**59%**	73%	**67%**

Table14. Percent with triple class virologic failure by years from start of HAART (patients naïve before HAART)

Observed data from ref 14. Modelled estimates based on ART start years 1997-2003 inclusive
Years from start of HAART

1		2		3		4		5		6	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
1%	**0%**	3%	**1%**	4%	**3%**	7%	**6%**	9%	**8%**	12%	**10%**

Table 15. Triple class failure (those with triple class failure before 2001, as in PLATO paper)

% ever previously with viral load < 500
Observed[15]: 50% model: **67%**

At time of triple class failure:-

	Observed[15]	model
median (IQR) viral load:	4.5 (3.9 - 5.0)	**4.2 (3.6 - 4.7)**
median (IQR) CD4:	199 (97 - 340)	**137 (44 - 259)**
median (IQR) CD4 nadir:	65 (17 - 169)	**41 (0 - 98)**
duration of ART (years):	4.7 (3.2 - 6.7)	**5.5 (4.3 - 8.0)**
% starting ART with $\geq$ 3 drugs	15%	**22%**

Table 16. Risk of resistance mutations (and virologic failure) after start of ART (patients starting with PI/r or NNRTI regimen)

% with at least one resistance mutation (and virologic failure)
observed data from ref 10.

Years from start of HAART												
1		2		3		4		5		6		7	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
4%	**12%**	7%	**16%**	10%	**19%**	12%	**21%**	14%	**22%**	16%	**24%**	19%	**25%**

Observed data underestimates because resistance tests not always performed at virologic failure.

Table 17. % with at least one resistance mutation for all three main classes (and virologic failure)
Years from start of HAART
(observed data from ref. 16).

1		2		3		4		5		6	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
		1.0%	**0.6%**			2.7%	**3.0%**			4.1%	**5.7%**

Table 18. Risk of resistance mutations after start of ART *

% with at least one resistance mutation

	Years from start of HAART					
	2		4		6	
	obs	mod[16]	obs	mod[16]	obs	mod[16]
M184V mutation (in those starting with 3TC)	6%	**10%**	13%	**14%**	18%	**17%**
TAM (in those starting with zdv or d4T)	4%	**7%**	9%	**10%**	13%	**12%**
PI mutation (in those starting with boosted PI regimen)	3%	**4%**	7%	**7%**	--	
NNRTI mutation (in those starting with NNRTI regimen)	8%	**15%**	14%	**19%**	21%	**22%**

*Observed data are likely to be under-estimates as resistance testing is not always performed at virologic failure

Table 19. Risk of death after triple class resistance

% dead by 3 years (for people with TCR up to 2004.5)	
Observed[17]	model
12%	**20%**

Table 20. Risk of death after triple class virologic failure
(oberved data from ref. 15).

Years from triple class failure (Triple class failure occurring before 2002)							
1		2		3		4	
obs	mod	obs	mod	obs	mod	obs	mod
5%	**9%**	10%	**17%**	15%	**24%**	21%	**27%**

REFERENCES

1. Collaborative Group on AIDS Incubation and Survival. Time from HIV-1 seroconversion to AIDS and death before widespread use of HAART: a collaborative re-analysi. Lancet 2000; 355: 1131-1137.

2. Touloumi G, Karafoulidou A, Gialeraki A, et al. Determinants of progression of HIV infection in a Greek hemophilia cohort followed for up to 16 years after seroconversion. JAIDS 1998; 19: 89-97.

3. Dorrucci, M; Rezza, G; Porter, K, et al. Temporal trends in postseroconversion CD4 cell count and HIV load: The Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration, 1985-2002. J Infect Dis 2007; 195:525-534.

4. Lundgren J, Pedersen C, Clumeck N, et al. Survival differences in European patients with AIDS, 1979-89. BMJ 1994; 308 (6936): 1068-1073.

5. Hubert J-P, Burgard M, Dussaix E, et al. Natural history of serum HIV-1 RNA levels in 330 patients with a known date of infection. AIDS 2000; 14:123-131.

6. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4(+) lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997; 126 (12): 946-954.

7. Phillips AN, Leford J, Sabin C, et al. Immunodeficiency and the risk of death in HIV infection. JAMA 1992; 268:2662-2666.

8. Egger M, May M, Chene G, et al. Prognosis of HIV-1 infected patients starting HAART: a collaborative analysis of prospective studies. Lancet 2002; 360:1178-.

9. Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet. 2005 5;366(9483):378-84.

10. Cozzi-Lepri A, Dunn D, Pillay D, et al. Long term probability of detecting HIV drug resistance in drug-naive patients starting currently recommended first line combination ART. Abstract 894,15th Conference on Retroviruses and Opportunistic Infections, Boston, USA, 3-6 Feb 2008.

11. Smith CJ, Phillips AN, Hill T, et al on behalf of the UK CHIC Study group. A cohort study of the rate of viral rebound after attainment of viral load below 50 copies/ml according to specific antiretroviral drugs in use. J Infect Dis 2005; 192(8):1387-97

12. Gallant J, Staszewski S, Pozniak A, et al. Efficacy and safety of Tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients. JAMA 2004; 292: 191-

13. Mocroft A et al. Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen : Increased incidence of stopping due to toxicity or patient/physician choice in patients with Hepatitis C co-infection. AIDS Res Hum Retr 2005; 21(9):743-52.

14. Mocroft A, Ledergerber B, Viard JP, et al. Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA Study Group. J Infect Dis 2004; 190: 1947-1956.

15. The PLATO collaboration. 2004. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet 364: 51-62.

16. UK HIV Drug Resistance Database and UK CHIC. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. AIDS 2005; 19 (5): 487-494.

17. Grover, D., *et al.* What is the risk of mortality following diagnosis of multi-drug resistant (MDR) HIV-1? Antimicrob Chem 2008; 61:705-713.