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Frequency and characteristics of long-term nonprogressors & HIV controllers in the Chelsea and Westminster HIV cohort

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Background

- In the vast majority of HIV-1 infected patients, a gradual decline in CD4+ T-cell count occurs throughout the course of HIV-1 infection
- This is accompanied by loss of immune responses
- Rate of disease progression from asymptomatic HIV-1 infection varies between HIV-1^{+} patients

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Background

Long-term nonprogressors (LTNP)

HIV-1+ patients maintain a stable CD4+ T-cell count within the normal range for a “long” time, who remain asymptomatic without antiretroviral therapy

HIV Controllers (HIC)

Subset of LTNP who suppress HIV-1 viral load below the limit of detection (BLD)

- These are an important groups of patients as they have a potential to provide an understanding of the way an individual is able to control HIV-1 without therapeutic intervention
- No internationally agreed definition of LTNP and HIC

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Background

- Some of many terminologies and criteria used to identify atypical patient groups in published literature

	Long term Survivor	HIV Controller	Viraemic controllers	Elite Controller	Elite Suppressor	Elite LTNP	LTNP	True LTNP
Duration of HIV-1 infection	≥8 years	≥10 years	Unspecified	Unspecified	Unspecified	≥8 years	≥8 years	≥10 years
CD4 T-cell count	≥500 cells/µl blood	Unspecified	Unspecified	Unspecified	Includes <500 cells/µl blood	≥600 cells/µl blood	>500 cells/µl blood	>500 cells/µl blood
CD4 T-cell slope	Decline <50 cells/µl blood per year	Unspecified	Unspecified	Unspecified	Unspecified	≥0 over prior 5 years	Unspecified	Non-declining
HIV-1 RNA plasma load	Unspecified	90% <400 copies/ml	<2000 copies/ml	<50 copies/ml	<50 copies/ml	Unspecified	Unspecified	Undetectable
Opportunistic infection	None	None	None	None	None	None	None	None
Antiretroviral therapy	None	None	None for ≥1 year	None for ≥1 year	None	None	None	None

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Aims

- To establish from the entire Chelsea and Westminster HIV cohort, number of HIV-1+ patients who fulfilled the criteria of;
  - **LTNP &**
  - **HIV Controllers**
- To estimate time to HIV-1 disease progression in identified patients

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Methods:
Chelsea and Westminster HIV Cohort criteria for selecting;

	LTNP	HIV Controller
Duration of HIV-1 infection	>7years	>7years
CD4 T-cell count	All within normal range *Cut off of >=450 cells/µl blood*	All within normal range *Cut off of >=450 cells/µl blood*
CD4 T-cell slope	>=0 since entry to cohort	>=0 since entry to cohort
HIV-1 RNA plasma load	All allowed (mostly low but detectable)	All BLD
Opportunistic infection	None	None
Antiretroviral therapy	None	None

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Methods

Study cohort
- 1st Jan 1988 – February 2010

Statistical methods
- MIXED procedure in SAS was used to create a random intercept model to derive a slope. Stable $CD4^+$ T-cell count was defined as patients whose $CD4^+$ T-cell count slope >=0
- Survival analyses was used to estimate time to HIV-1 progression and data were censored at the most recent visit to the clinic

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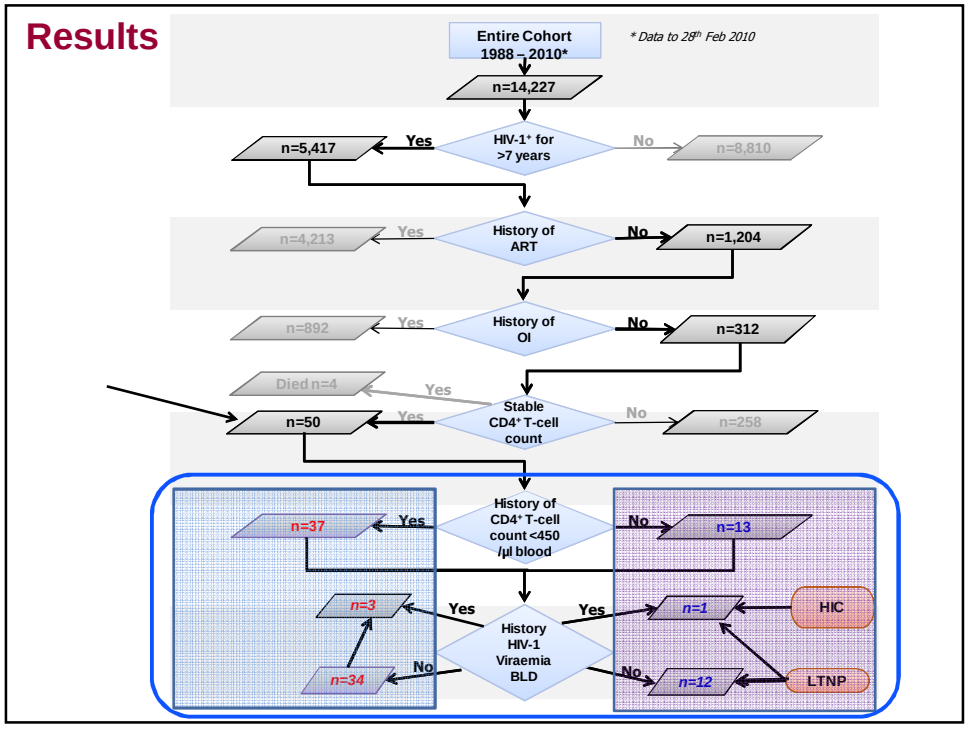
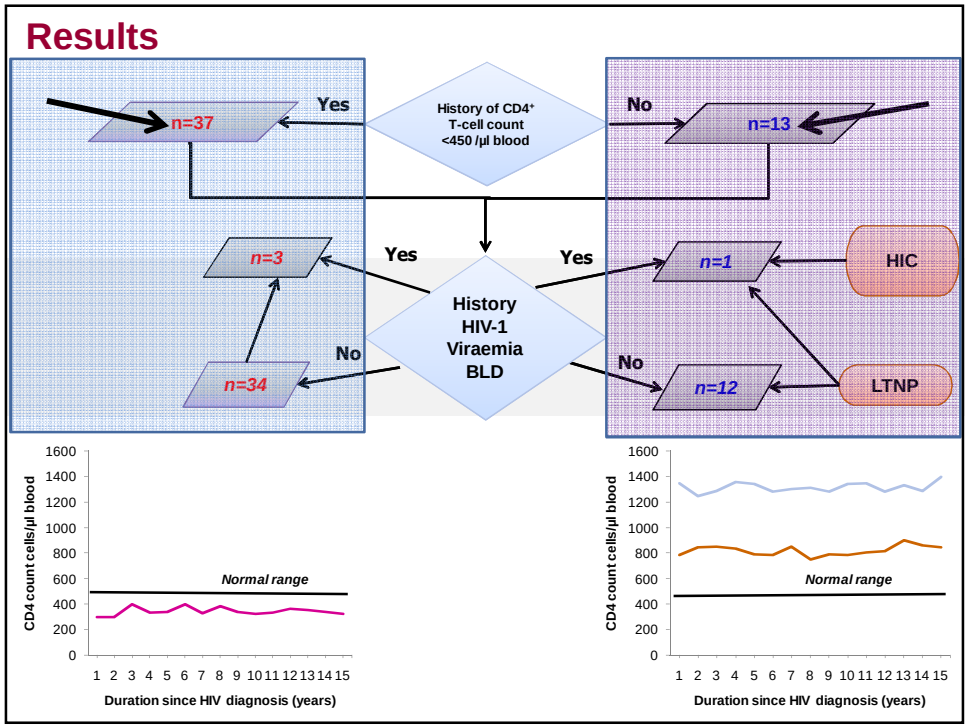
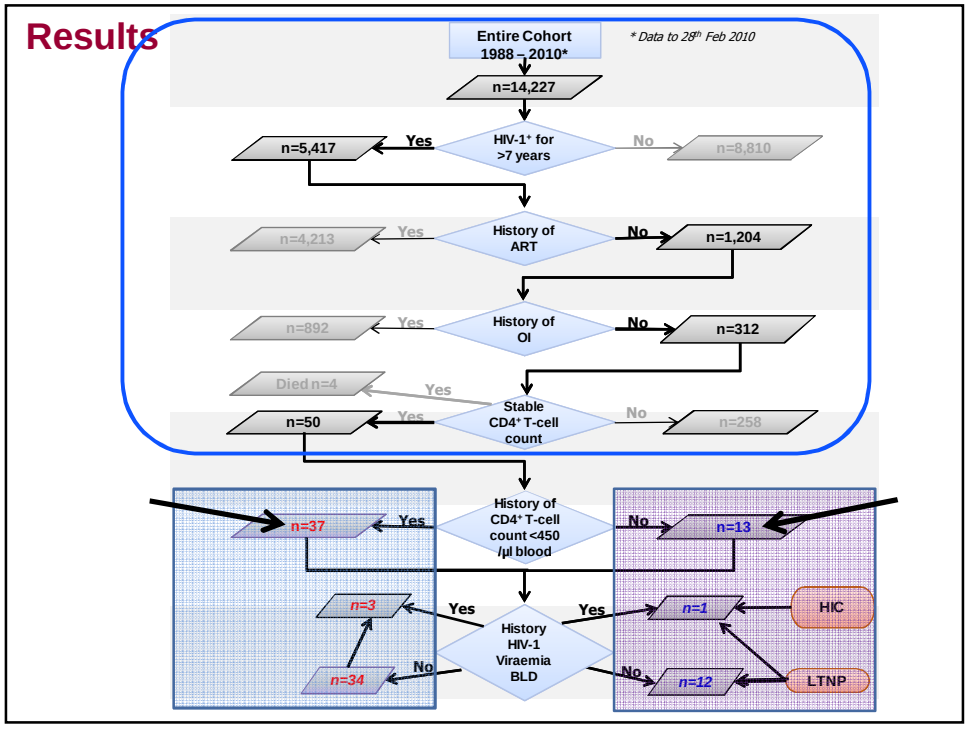
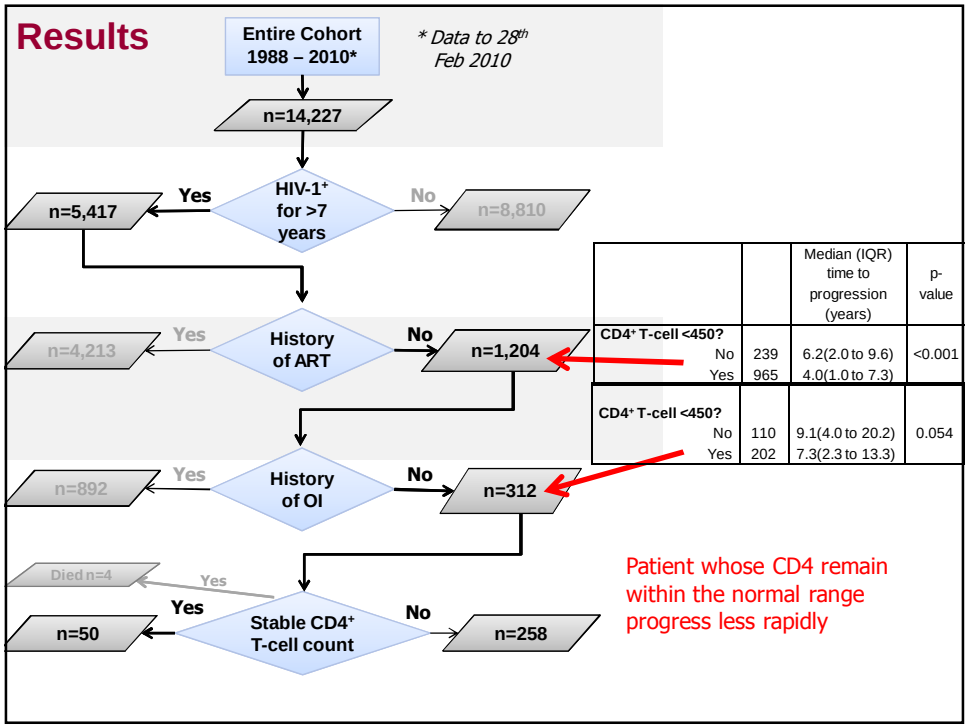

Results
Entire Cohort 1988 – 2010*
* Data to 28th Feb 2010
n=14,227
HIV-1+ for >7 years
Yes
n=5,417
No
n=8,810
History of ART
Yes
n=4,213
No
n=1,204
History of OI
Yes
n=892
No
n=312
Stable CD4+ T-cell count
Yes
Died n=4
Yes
n=50
No
n=258
History of CD4+ T-cell count <450 /µl blood
Yes
n=37
No
n=13
History HIV-1 Viraemia BLD
Yes
n=3
Yes
n=1
HIC
No
n=34
No
n=12
LTNP


Results
History of CD4+ T-cell count <450 /µl blood
Yes
n=37
No
n=13
History HIV-1 Viraemia BLD
Yes
n=3
Yes
n=1
HIC
No
n=34
No
n=12
LTNP
CD4 count cells/µl blood
Normal range
Duration since HIV diagnosis (years)
CD4 count cells/µl blood
Normal range
Duration since HIV diagnosis (years)





		Median (IQR) time to progression (years)	p-value
CD4+ T-cell <450?			
No	239	6.2(2.0 to 9.6)	<0.001
Yes	965	4.0(1.0 to 7.3)	
CD4+ T-cell <450?			
No	110	9.1(4.0 to 20.2)	0.054
Yes	202	7.3(2.3 to 13.3)	

Limitations

- Like other observational databases patients are lost to follow up and this may be more frequent occurrence in patients whose HIV-1 infection is clinically stable
- Only 0.38% of the entire HIV cohort were identified with atypical characteristics. This figure concurs with a large HIV-1$^+$ cohort in France (0.4%) however they used a slightly different selection criteria to identify the LTNP
- With different criteria used to identify these atypical patient group means immunological, virological and genetic markers cannot be accurately compared between studies

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Conclusion

- Studies on LTNP have used varying selection criteria and varying definitions of rate of CD4$^+$ T-cell count decline to identify these patients. We used a stringent criteria as non-declining CD4$^+$ T-cell count since cohort entry
- Only 0.38% of atypical patients were identified from the entire Chelsea and Westminster HIV cohort
- Most HIV infected patients will eventually progress (symptoms, CD4, VL)
- A need exists for an internationally agreed standardised use of terminologies and definitions

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Acknowledgements

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