TAHOD-LITE: Antiretroviral Treatment for Adult HIV Infection in Asia, 1998 to 2013

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TAHOD-LITE: Antiretroviral Treatment for Adult HIV Infection in Asia, 1998 to 2013

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Abbreviations

3TC/FTC	lamivudine/emtricitabine
ABC	Abacavir
ART	Antiretroviral therapy
ATV	Atazanavir
AZT	Zidovudine
CI	Confidence interval
d4T	Stavudine
EFV	Efavirenz
HR	Hazard ratio
IDU	Injecting drug user
LPV	Lopinavir
LTFU	Lost to follow up
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PI	Protease inhibitor
pys	person-years
TAHOD	TREAT Asia HIV Observational Database
TAHOD-LITE	TREAT Asia HIV Observational Database Low Intensity Transfer
TDF	Tenofovir
VL	HIV viral load

1. Executive Summary

The TREAT Asia HIV Observational Database (TAHOD) has recruited 9000 HIV-infected adult patients, with nearly 6,000 patients in active follow up, from 21 sites across the Asia Pacific region. While the study collects a fairly rich dataset, patients are not randomly selected, and so patterns of treatment and care may not be fully representative of the wider clinical population.

The TREAT Asia HIV Observational Database Low Intensity Transfer (TAHOD-LITE), an extension of TAHOD, address this limitation by collecting data from all HIV-infected patients who have attended care at some of the TAHOD sites, thus acting more as a surveillance system. This study is much larger and representative, allowing questions around ART use, durability and treatment outcomes to be addressed more reliably.

The TAHOD-LITE data in this report comprises of 30 153 patients from 6 Asia-Pacific countries. Over 60% of patients from eachcountryare male, with the exception of Cambodia where 47% are male. Between 60-93% of patients from each country had heterosexual contact as the main mode of HIV exposure, excluding Hong Kong and Singapore where approximately 50% are through heterosexual contact and 30% are through homosexual contact. There were 18 842 patients who started antiretroviral therapy (ART)defined as a regimen with 3 or more ARV drugs, with 4% of patients undertaking a previous mono or duo regimen. The proportion with a missing first CD4 result for all patients and pre-treatment CD4 result for ART patients has reduced over time. There are also greater proportions of ART patients with a baseline CD4 between 201-350 cells/μL and reduced proportions with ≤200cells/μLsince 2005. The crude CD4 testing rate across all countries was 1.8person-years (pys) with 95% CI (1.82-1.84). Most countries had increases in testing rates from earlier time periods.

For most countries, a large proportion of all patients did not have a viral load test conducted while in care. A majority of ART patients did not have a viral load test prior to ART initiation, with the exception of patients from Hong Kong and Singapore. Across all the countries and time periods, the crude rate of viral load testing was 0.6 pys with 95% CI (0.61-0.62). Overall, stavudine (d4T) use in initial ART has declined since 2003-2005, coinciding with an increase in tenofovir (TDF), zidovudine (AZT) and abacavir (ABC) use. In 2010-2013, efavirenz (EFV) use was greater than 60% across all countries and surpassed nevirapine (NVP)at ≤40%; however the proportion of patients starting NVP was close to 80% for Cambodia and Indonesia. Risk factors associated with treatment modification included later period of ART initiation, female sex, low pre-treatment CD4 count, first regimen not containing a non-nucleoside reverse transcriptase inhibitor

(NNRTI) and previous mono/duo exposure. d4T use has also declined in second ARTsince 2003-2005 accompanied with an increase in TDF and ABC. In all countries, use of a protease inhibitor (PI) is uncommon though atazanavir (ATV) and lopinavir (LPV) use is increasing. Time to second treatment switch occurred sooner in Hong Kong, Singapore and India. Earlier period of ART initiation, younger age, mode of HIV exposure other than unknown/other, low pre-treatment CD4 count, second regimen not containing a PI and previous mono/duo were all risk factors associated with second treatment modification. Overall survival from ART initiation had improved over time. Significant risk factors associated with poorer survival include earlier years of ART initiation, older age at ART initiation, male gender, injecting drug use mode of HIV exposure, lower pre-ART CD4 cell count, first regimen containing nucleoside reverse transciptase inhibitor (NRTI) and a PI, and previous mono/duo exposure. Lost to follow up (LTFU) rates appeared to be greater in more recent time periods, probably reflecting greater transfer of patients. Factors associated with increased risk of LTFU include year of ART initiation, younger age, male gender, injecting drug use mode of HIV exposure, lower pre-ART CD4 cell count, no previous mono/duo exposure and hepatitis C co-infection.

2. Introduction

TAHOD is an observational cohort that has, since its inception in 2003, recruited 9000 HIV-infected adult patients, with nearly 6,000 patients in active follow up, from 21 sites across the Asia Pacific region. The study collects a fairly rich dataset including demographic, clinical and treatment data. However, patients are not randomly selected and recruited, so patterns of treatment and care may not be fully representative of the wider clinical population.

TAHOD-LITE, an extension of TAHOD, was proposed to address this limitation by collecting data from all HIV-infected patients who have attended care at some of the TAHOD sites, thus acting more as a surveillance system. This study is much larger, and focuses on a simplified dataset consisting of basic demographics, clinical biomarkers and treatment data that will allow TAHOD- LITE to address more reliably questions around ART use, durability and treatment outcomes.

2.1 TAHOD-LITE sites

TAHOD-LITE consists of 7 sites from 6 Asia-Pacific countries including: Bach Mai Hospital, Hanoi, Vietnam; National Hospital of Tropical Diseases, Hanoi, Vietnam; the Social Health Clinic, National Centre for HIV/AIDS/Dermatology and STDs, Phnom Penh, Cambodia; Queen Elizabeth Hospital, Hong Kong, China; Sanglah Hospital, Denpasar, Indonesia; Tan Tock Seng Hospital, Singapore; Y.R. GaitondeCenter for AIDS Research & Education (YRG Care), Pune, India.

2.2 Methods

All patients in TAHOD-LITE were included in the summary of first clinic attendees' analysis if they were aged ≥18 years at first clinic visit. For all other analyses, only patients who satisfy the above criteria and have started an ART regimen with 3 or more drugs from 1998 to 2013 were included. Furthermore, patients were excluded if their first ART initiation was prior to the following years representing time periods of complete patient sampling, for their respective site/country: Cambodia 2004; Hong Kong 2003; Indonesia 2003, Singapore 2006, Vietnam 2010 (Bach Mai Hospital only).

3. Patients at first clinic attendance

- Characteristics of all patients.
- First CD4 cell count.
- First HIV viral load.

3.1 Methods

The characteristics of all patients are summarizedin Table 1 (n=30153). Only patients from TAHOD-LITE that are aged ≥18 years at first clinic visit are included. First clinic attendance is defined as the cohort date for patients from TAHOD, or as the date of the first lab result prior to first ART initiation or date of the most recent clinic visit for patients from TAHOD-LITE. The proportions of first CD4 cell count for each country and for all countriesby time period are presented as histograms in Figure 1and Figure 2. The proportions of first HIV viral load for each country and for all countriesby time period are summarized in Figure 3 and Figure 4. The first CD4 and HIV viral load is defined as the first lab result prior to the initiation of the first regimen.

3.2 Summary of results

Overall, there have been decreased proportions of patients with missing first CD4 cell count coinciding with increased proportions of patients with first CD4 cell count ≤100 cells/μLsince 2001. Cambodia and Hong Kong have had increasing proportions with missing first CD4 cell count.Whilst India has the greatest proportion with a missing first CD4 cell count, however many patients are seen once and transferred elsewhere.

All countries had a majority of the patients with a missing first HIV viral load, with the exception of high income countries (Hong Kong and Singapore) and Vietnam, in recent years. There have been increased proportions of patients from high income countries with a first HIV viral load, particularly in recent years, but relatively little change in other countries.Cambodia has had nearly all patients missing a first HIV viral load. Vietnam has had a drastic increase, in 2012/13, in patients with a first HIV viral load. Overall, there has been a slightly decreasing proportion of patients with a missing baseline HIV viral load and the majority of the patients with a baseline HIV viral load had viraemia ≥400 copies/mL.

Table 1. Overview of characteristics of all the patients seen at first clinic attendance, for each country and for all countries.

	Cambodia n=3470		Hong Kong n=1142		India n=19302		Indonesia n=1390		Singapore n=2291		Vietnam n=2558		Overall n=30153	
	Total	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**
Age, years														
≤30	1200	(35)	244	(21)	7177	(37)	621	(45)	530	(23)	1022	(40)	10695	(35)
31-40	1443	(42)	417	(37)	8168	(42)	532	(38)	656	(29)	1154	(45)	12425	(41)
41-50	589	(17)	291	(25)	2905	(15)	176	(13)	584	(25)	237	(9)	4813	(16)
51+	238	(7)	190	(17)	1052	(5)	61	(4)	521	(23)	145	(6)	2220	(7)
Median [IQR]	34	[29, 41]	39	[32, 47]	34	[28, 40]	32	[28, 38]	40	[32, 50]	33	[29, 37]	34	[29, 40]
Sex														
Male	1645	(47)	923	(81)	12643	(66)	906	(65)	2108	(92)	1637	(64)	19862	(66)
Female	1820	(52)	218	(19)	6643	(34)	482	(35)	180	(8)	921	(36)	10264	(34)
Transgender	5	(<0.1)	1	(<0.1)	16	(<0.1)	2	(<0.1)	3	(<0.1)	0	(-)	27	(<0.1)
HIV exposure category														
Heterosexual contact	3127	(90)	510	(45)	17881	(93)	1049	(75)	1142	(50)	1542	(60)	25251	(84)
Homosexual contact	31	(1)	404	(35)	70	(<0.4)	87	(6)	761	(33)	23	(1)	1376	(5)
Injecting drug use only	13	(<0.4)	49	(4)	300	(2)	175	(13)	73	(3)	837	(33)	1447	(5)
Blood products	24	(1)	11	(1)	563	(3)	0	(-)	1	(<0.1)	3	(<0.1)	602	(2)
Bisexual	3	(<0.1)	62	(5)	171	(1)	3	(<0.2)	217	(9)	1	(<0.1)	457	(2)
Other/Unknown	272	(8)	106	(9)	317	(2)	76	(5)	97	(4)	152	(6)	1020	(3)
Hepatitis B Co Infection[†]														
Negative	2327	(67)	903	(79)	314	(2)	536	(39)	1917	(84)	1230	(48)	7227	(24)
Positive	285	(8)	110	(10)	15	(<0.1)	51	(4)	178	(8)	194	(8)	833	(3)
Not Tested	858	(25)	129	(11)	18973	(98)	803	(58)	196	(9)	1134	(44)	22093	(73)
Hepatitis C Co infection[†]														
Negative	2438	(70)	903	(79)	2159	(11)	469	(34)	2002	(87)	1431	(56)	9402	(31)
Positive	150	(4)	78	(7)	262	(1)	76	(5)	96	(4)	1065	(42)	1727	(6)
Not Tested	882	(25)	161	(14)	16881	(87)	845	(61)	193	(8)	62	(2)	19024	(63)
Patients seen only once	125	(4)	64	(6)	5420	(28)	70	(5)	32	(1)	35	(1)	6230	(21)

[†] HBV is result from HBV surface antigen test and HCV is result from HCV antibody test.

Figure 1.First CD4+ T-cell count (cells/μL) for each country by the year of the test date.

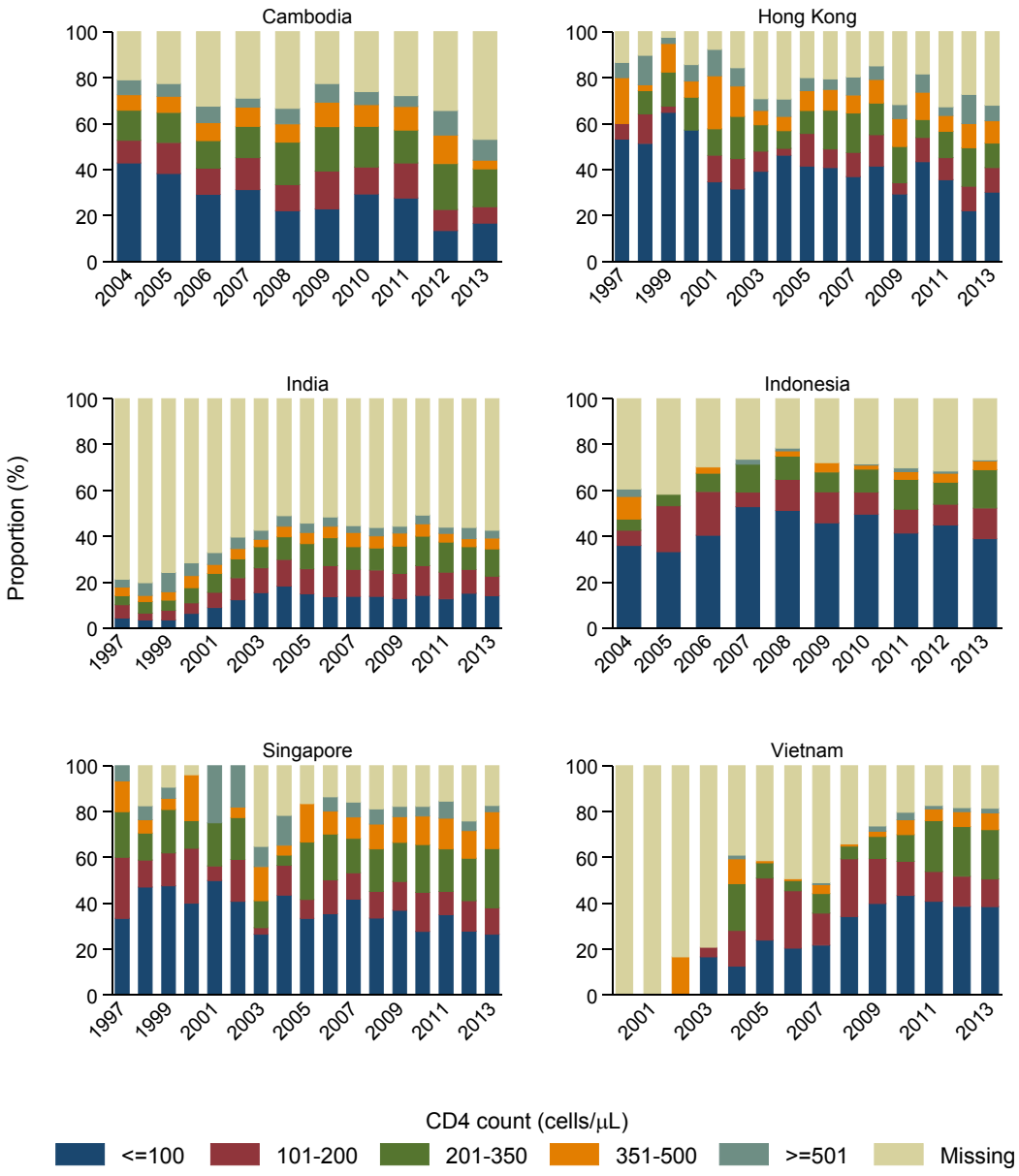


Figure 2. First CD4+ T-cell count (cells/µL) for all countries by the year of the test date.

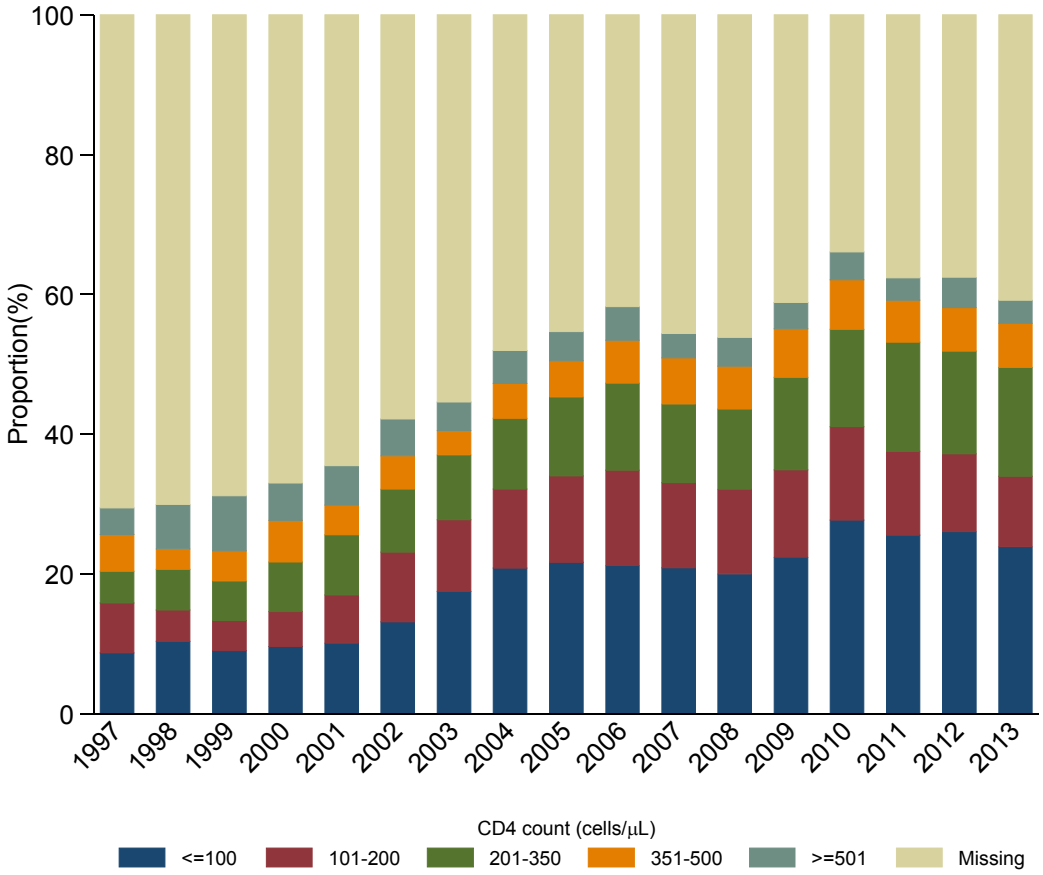


Figure 3.FirstHIV viral load (copies/mL) for each country by the year of the test date.

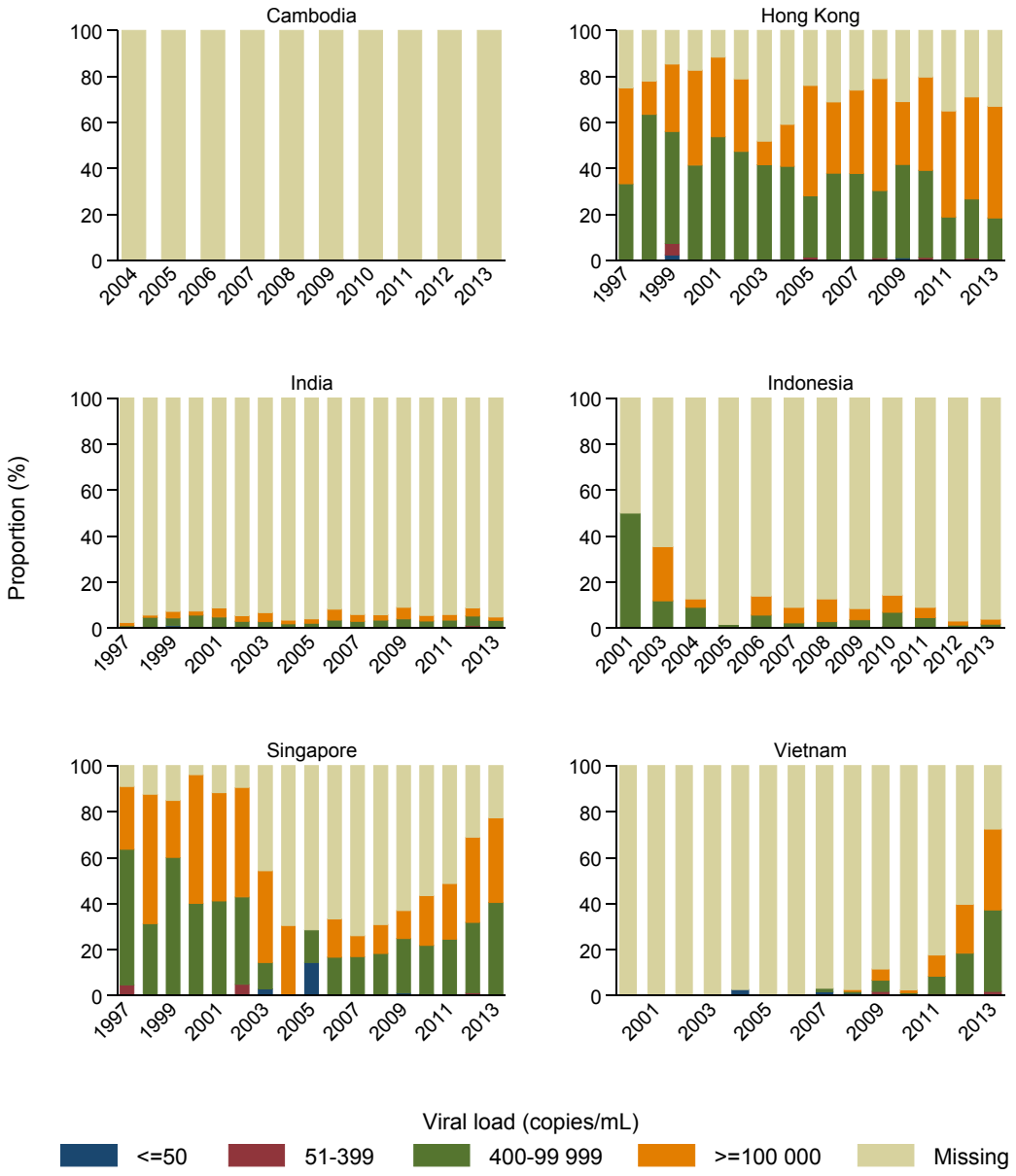
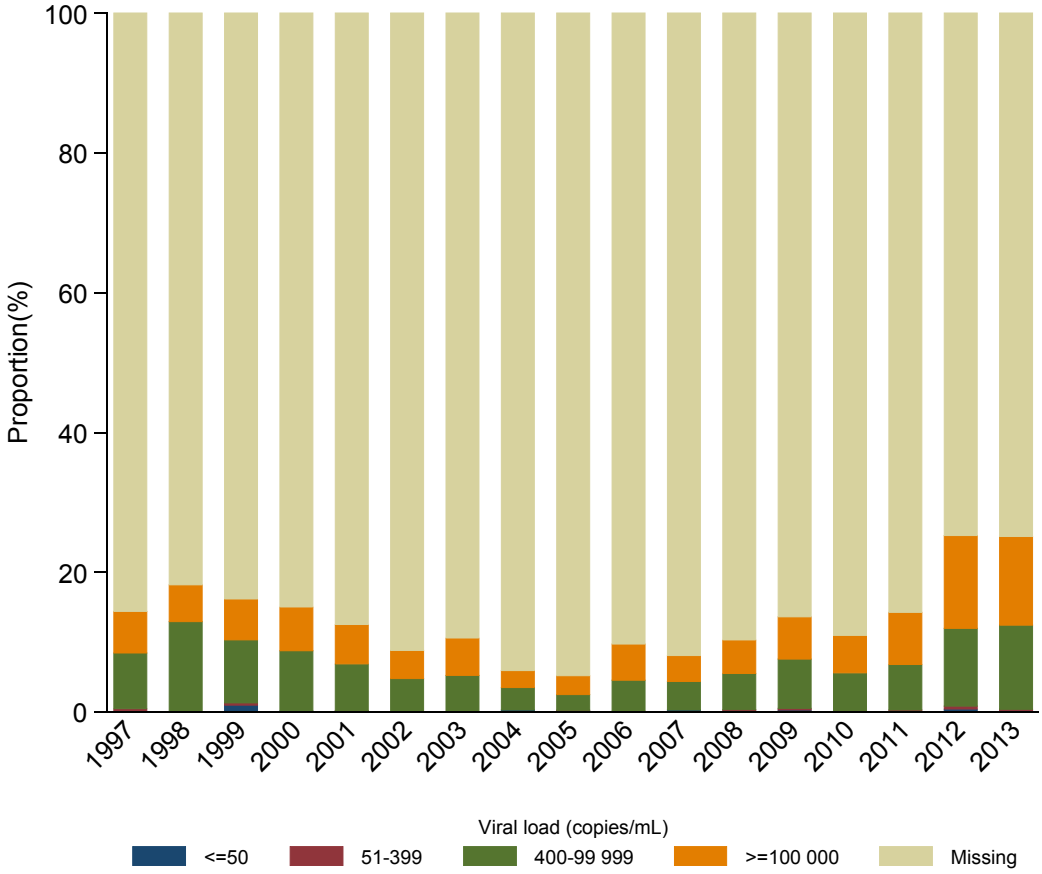


Figure 4.FirstHIV viral load (copies/mL) for all countries by the year of the test date.



4. Patients who start ART

- Characteristics of all patients who have started ART.
- Baseline CD4 cell count.
- Baseline HIV viral load.

4.1 Methods

The characteristics of all patients who have started ART are summarized in Table 2 (n=18842). Patients who started a regimen with 3 or more drugs from 1998 to 2013 are presented. Age is at the date of the first ART. Baseline CD4 cell count for each country and for all countriesby time period are presented as histograms in Figure 5 and Figure 6. Baseline HIV viral load for each country and for all countriesby time period are presented in Figure 7 and Figure 8. The baseline CD4 and HIV viral load is defined as the most recent lab result within 6 months prior to initiating the first regimen.

4.2 Summary of results

Overall, since 2005, there have been decreasing proportions of patients with baseline CD4 cell count ≤200 cells/μL and increasing proportions of patients with baseline CD4 cell count ≥201. The proportion of patients with a missing baseline CD4 cell count has also decreased with time.

All countries had a majority of the patients with a missing baseline HIV viral load, with the exception of high income countries (Hong Kong and Singapore) and Vietnam in more recent years. The high income countries have had decreasing proportions of patients with a missing HIV viral load over time, whilst all other countries have had relatively little change. Vietnam has had a drastic increase in the proportion of patients with a baseline HIV viral load for 2012/2013. Overall, there have been a decreasing proportion of patients with a missing baseline HIV viral load in recent years. The majority of the patients with a baseline HIV viral load had viraemia ≥400 copies/mL.

Table 2.Overview of characteristics of all the patients who have started ART, for each country and for all countries.

	Cambodia n=2539		Hong Kong n=794		India n=10394		Indonesia n=1116		Singapore n=1816		Vietnam n=2183		Overall n=18842	
	Total	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**	**Total**	**(%)**
Age, years														
≤30	791	(31)	161	(20)	2690	(26)	513	(46)	321	(18)	907	(42)	5383	(29)
31-40	1129	(44)	276	(35)	5090	(49)	424	(38)	523	(29)	948	(43)	8390	(45)
41-50	449	(18)	218	(27)	1947	(19)	136	(12)	502	(28)	202	(9)	3454	(18)
51+	170	(7)	139	(18)	667	(6)	43	(4)	470	(26)	126	(6)	1615	(9)
Median [IQR]	35	[30, 41]	40	[32, 48]	35	[31, 41]	32	[28, 38]	42	[34, 51]	32	[28, 37]	35	[30, 42]
Sex														
Male	1220	(48)	645	(81)	7289	(70)	742	(66)	1683	(93)	1390	(64)	12969	(69)
Female	1316	(52)	148	(19)	3095	(30)	372	(33)	131	(7)	793	(36)	5855	(31)
Transgender	3	(<0.1)	1	(<0.1)	10	(<0.1)	2	(<0.2)	2	(<0.1)	0	(-)	18	(<0.1)
HIV exposure category														
Heterosexual contact	2357	(93)	334	(42)	9681	(93)	828	(74)	905	(50)	1351	(62)	15456	(82)
Homosexual contact	23	(1)	329	(41)	45	(<0.4)	71	(6)	611	(34)	18	(1)	1097	(6)
Injecting drug use only	7	(<0.3)	29	(4)	61	(1)	157	(14)	62	(3)	675	(31)	991	(5)
Blood products	18	(1)	5	(1)	377	(4)	0	(-)	0	(-)	3	(<0.1)	403	(2)
Bisexual	3	(<0.1)	57	(7)	109	(1)	3	(<0.3)	178	(10)	1	(<0.1)	351	(2)
Other/Unknown	131	(5)	40	(5)	121	(1)	57	(5)	60	(3)	135	(6)	544	(3)
Hepatitis B Co Infection[†]														
Negative	2058	(81)	675	(85)	281	(3)	410	(37)	1522	(84)	1009	(46)	5955	(32)
Positive	242	(10)	76	(10)	14	(<0.1)	41	(4)	145	(8)	153	(7)	671	(4)
Not Tested	239	(9)	43	(5)	10099	(97)	665	(60)	149	(8)	1021	(47)	12216	(65)
Hepatitis C Co infection[†]														
Negative	2140	(84)	677	(85)	1547	(15)	352	(32)	1600	(88)	1248	(57)	7564	(40)
Positive	137	(5)	51	(6)	71	(1)	70	(6)	79	(4)	886	(41)	1294	(7)
Not Tested	262	(10)	66	(8)	8776	(84)	694	(62)	137	(8)	49	(2)	9984	(53)
Previous Mono/Duo	22	(1)	49	(6)	577	(6)	40	(4)	35	(2)	74	(3)	797	(4)
Excluded mono/duo only	68		6		593		3		3		2		675	

[†]HBV is result from HBV surface antigen test and HCV is result from HCV antibody test.

Figure 5.Baseline CD4+ T-cell count (cells/μL) for each country by the year of the test date.

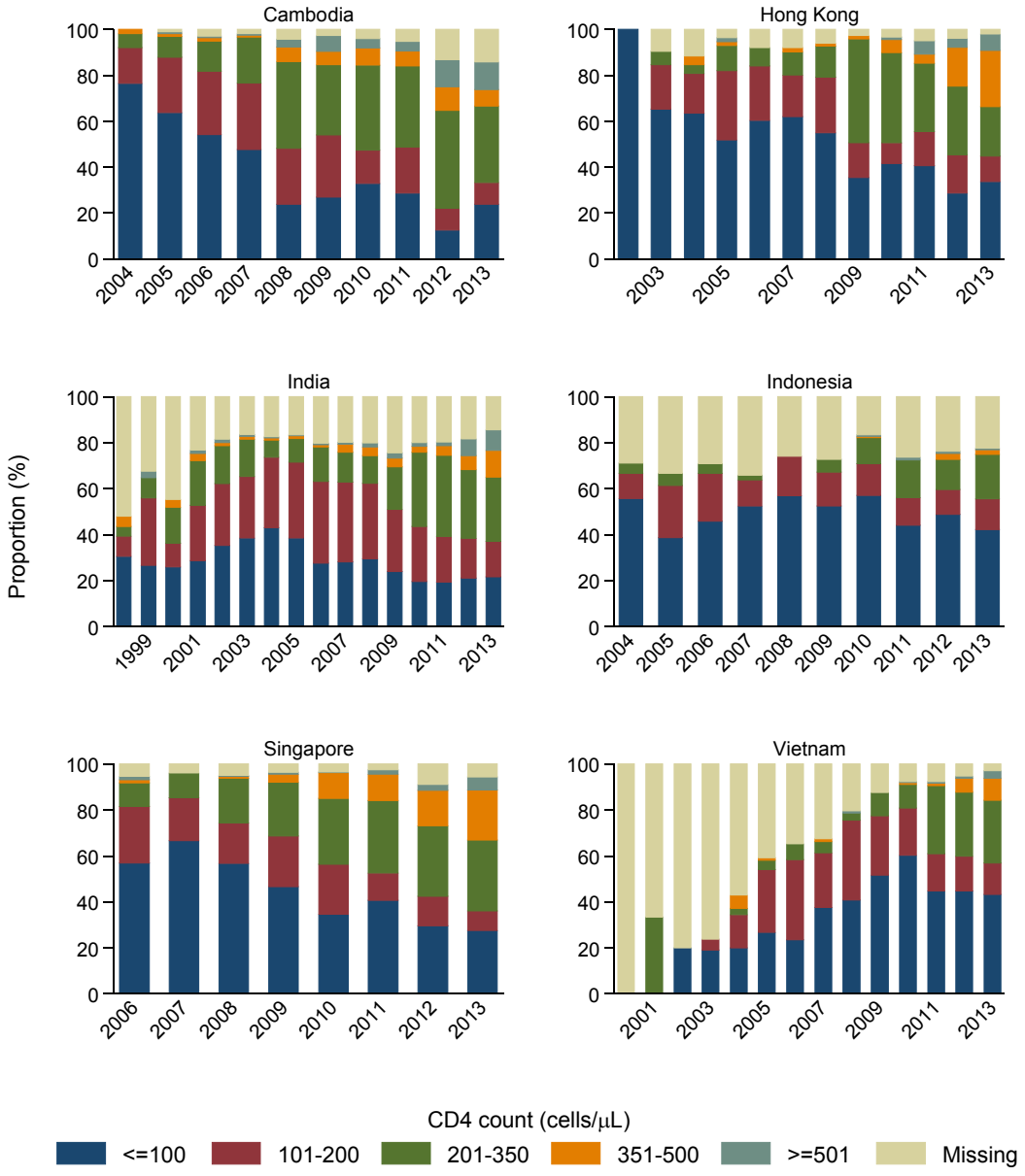


Figure 6.Baseline CD4+ T-cell count (cells/µL) for all countries by the year of the test date.

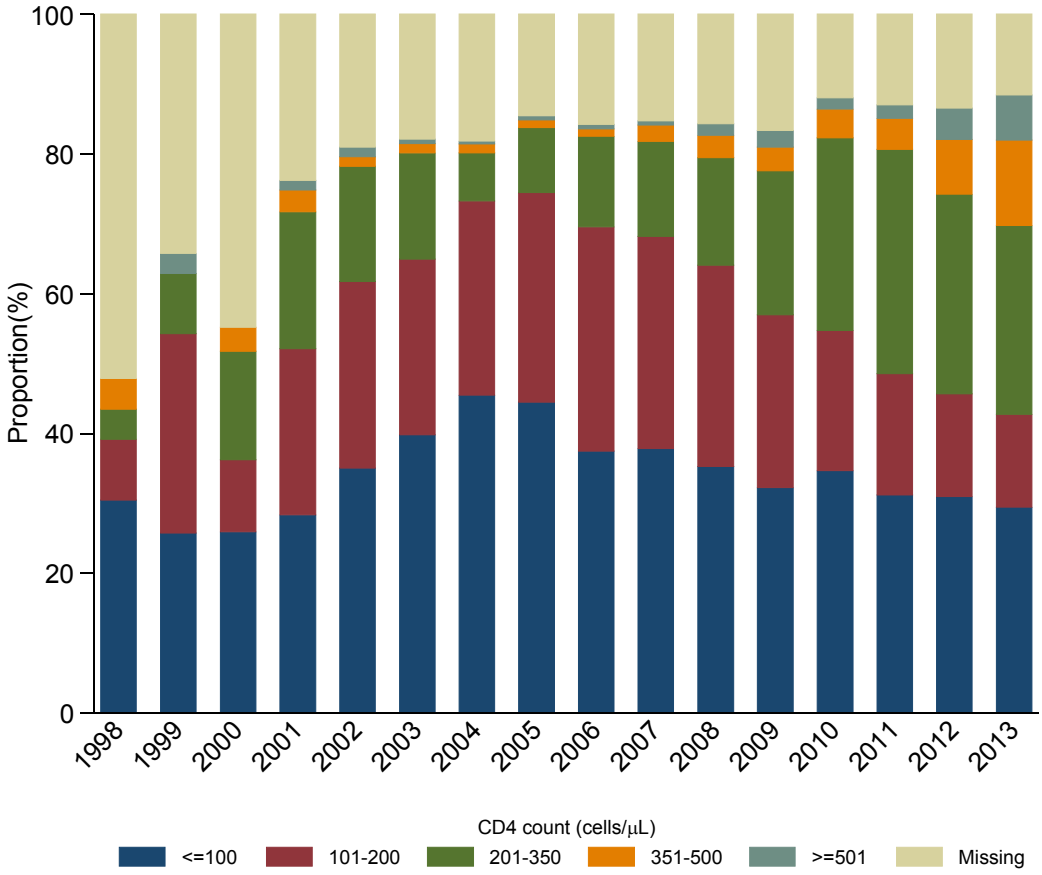


Figure 7.Baseline HIV viral load (copies/mL) for each country by the year of the test date.

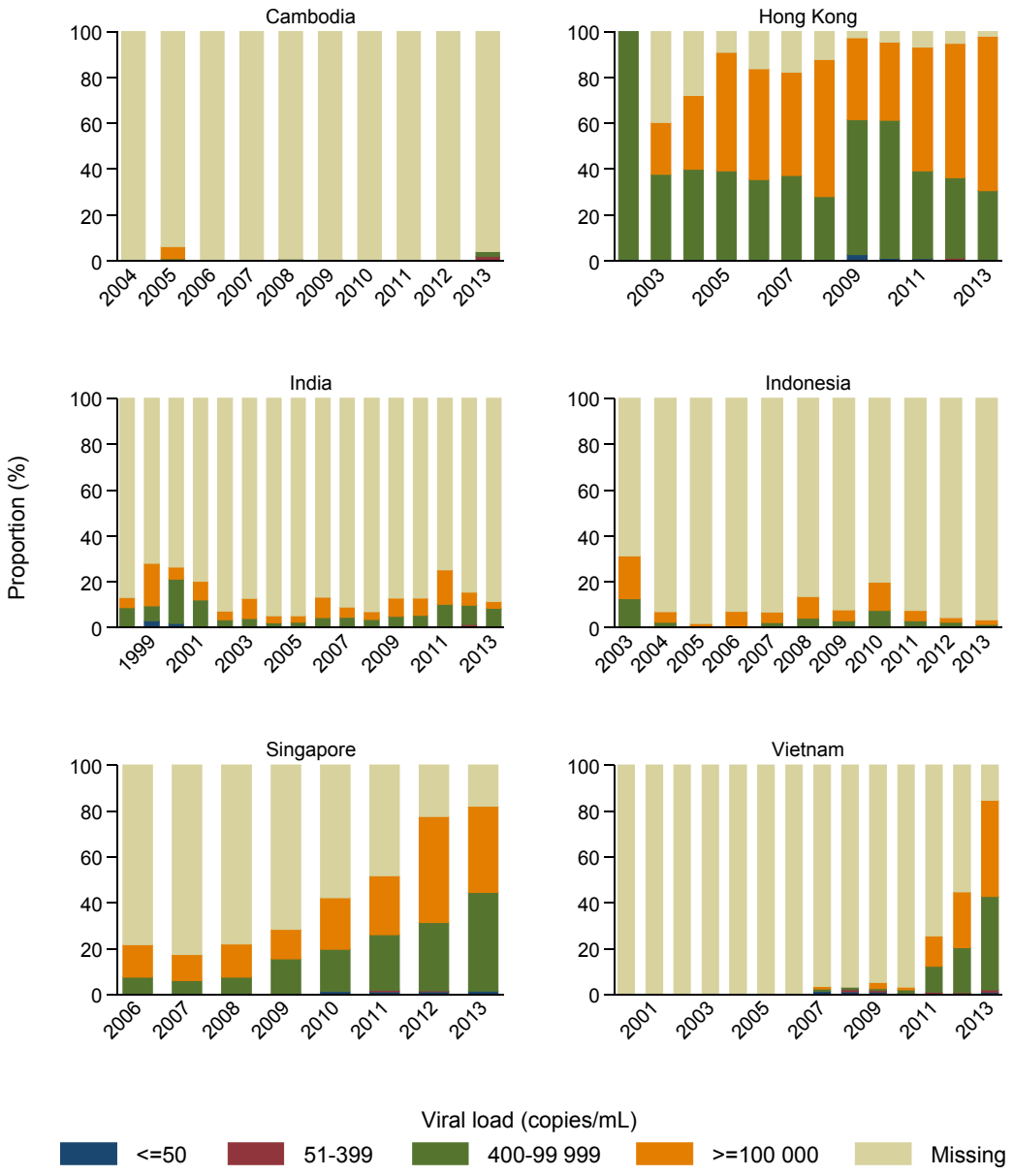
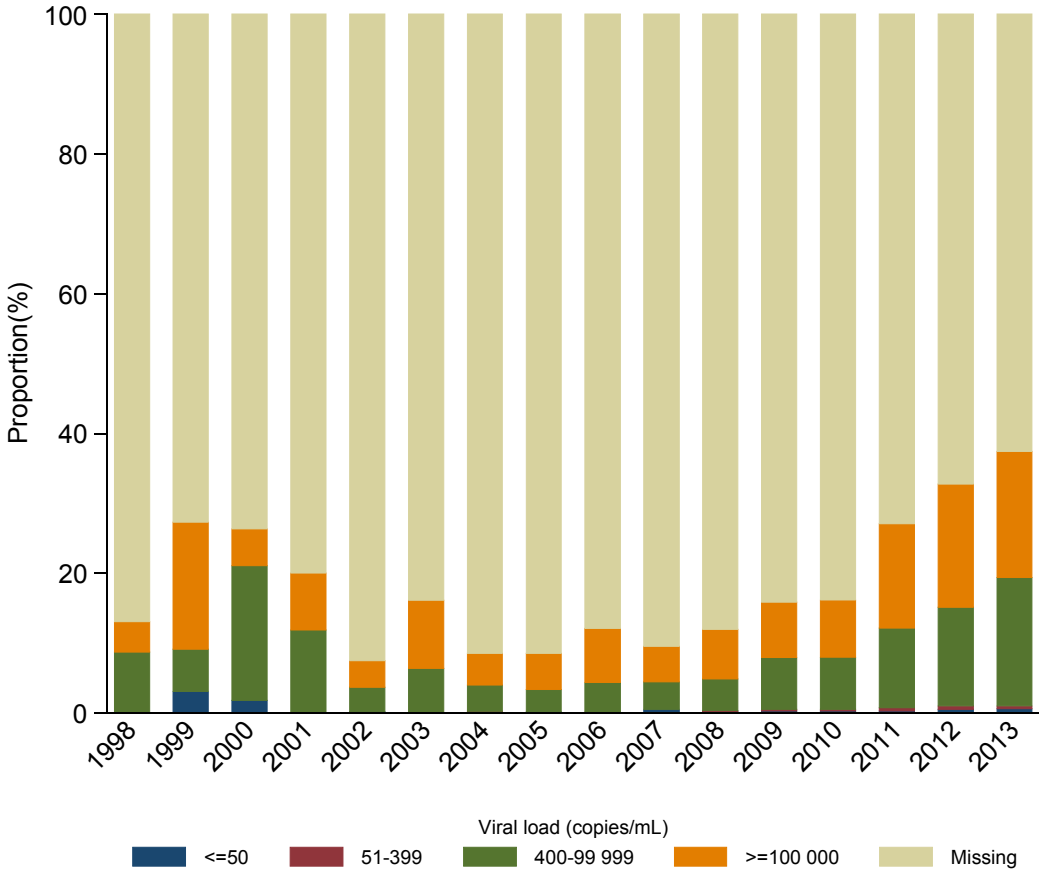


Figure 8.Baseline HIV viral load (copies/mL) for all countries by the year of the test date.



5. First ART

- First regimen NRTI combination
- First regimen NNRTI
- Mortality on first regimen
- Durability of first regimen
- Risk factors associated with switch to second regimen

5.1 Methods

First combination ART was defined as the first triple combination. The proportions of patients starting an antiretroviral/antiretroviral combination by period are presented in Figure 9 to Figure 12. Switch to second ART was considered to be a change of drug class or a change of two or more drugs. Mortality on first regimen and durability of the first regimen were evaluated using Kaplan-Meier curves (Figure 13 to Figure 16). Risk factors for treatment switch were assessed using Cox regression models stratified by site. The multivariate model is adjusted for all variables shown (Table 3).

5.2 Summary of results

Overall, 18,842 patients started first-line ART. Use of d4T declined substantially after 2003-05 coinciding with an increase in TDF, AZT and ABC use. However, rates of d4T initiation remained >15% in Vietnam, India and Cambodia in 2010-13. EFV use surpassed that of NVP in 2010-13 in the combined analysis, although the proportion of patients starting NVP was close to 80% in the same period for Cambodia and Indonesia.

Mortality rates were highest in earlier time periods. Time to first treatment switch was quickest in higher income countries (Hong Kong and Singapore) and India. Significant risk factors associated with treatment modification were later period of ART initiation, female sex, low baseline CD4 cell count, first regimen not containing an NNRTI, and previous mono/duo exposure.

Figure 9.First regimen NRTI combination for each country by time period.

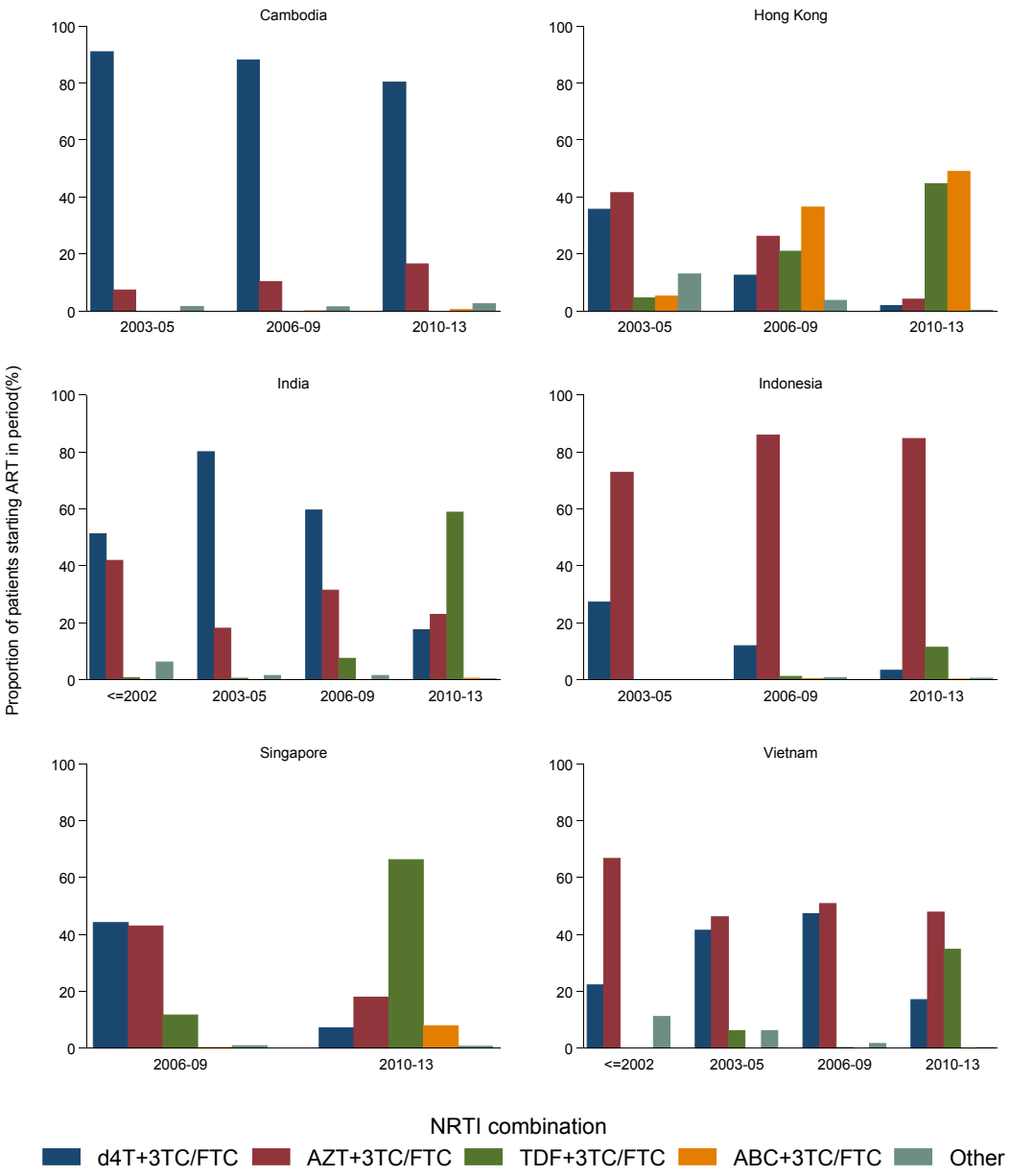


Figure 10.First regimen NRTI combination for all countriesby time period.

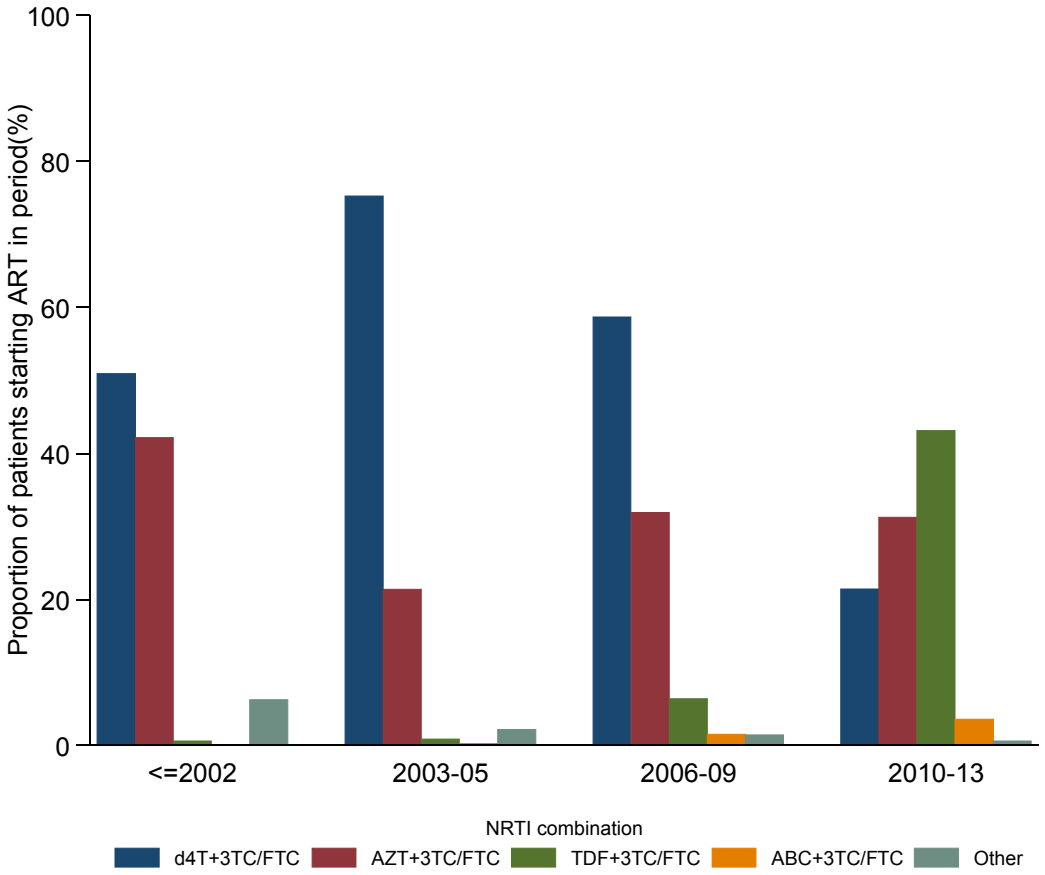


Figure 11.First regimen NNRTI for each country by time period.

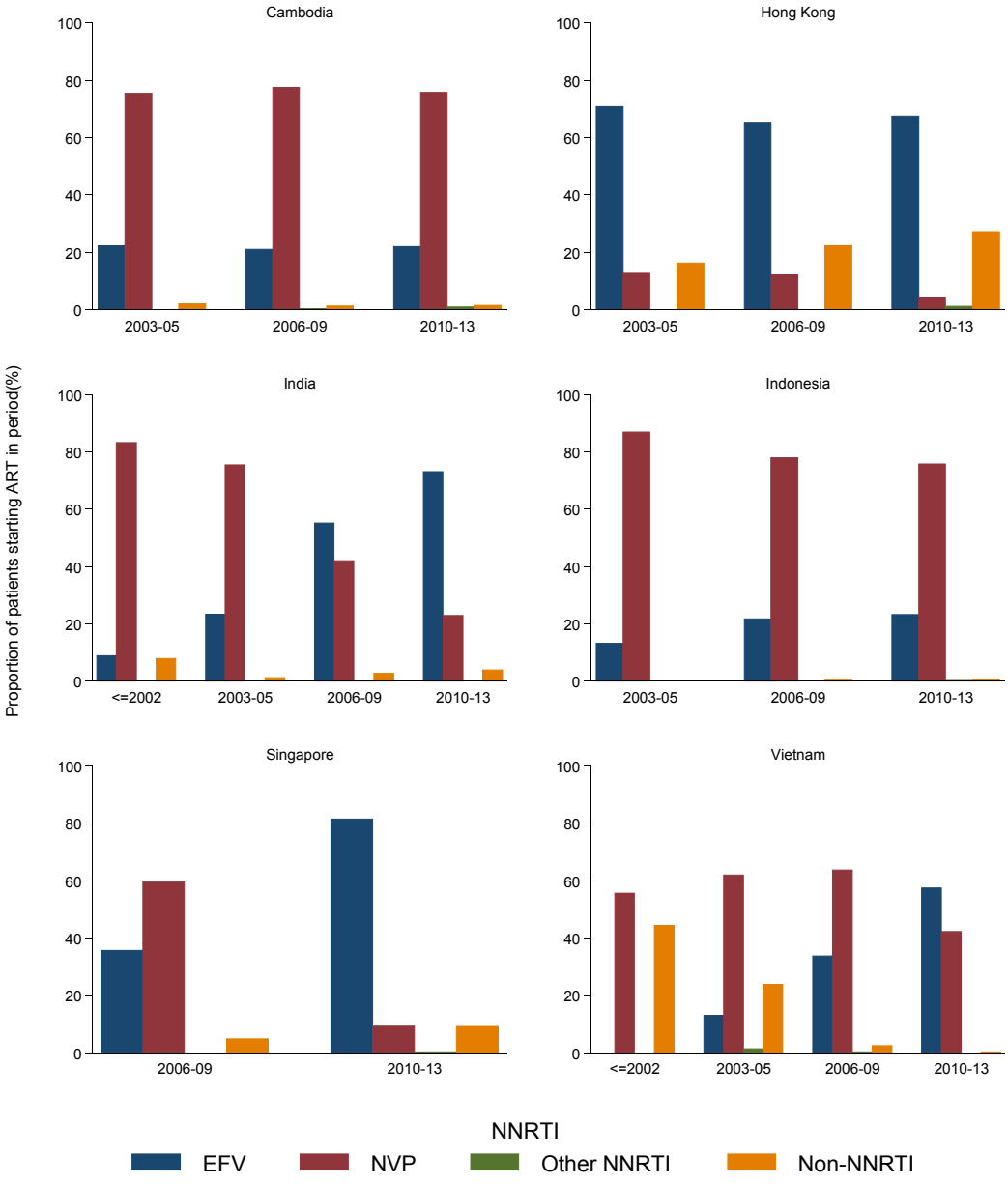


Figure 12.First regimen NNRTI for all countriesby time period.

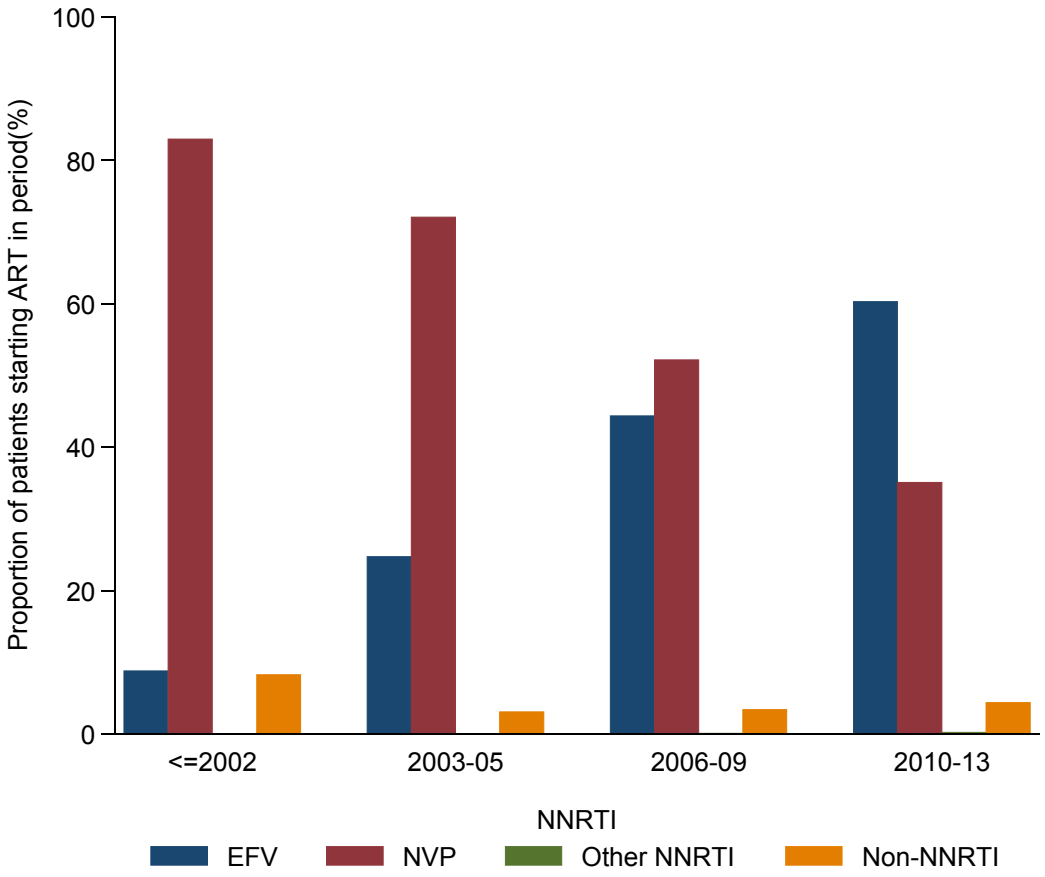


Figure 13.Mortality on first ART for each country by time period.

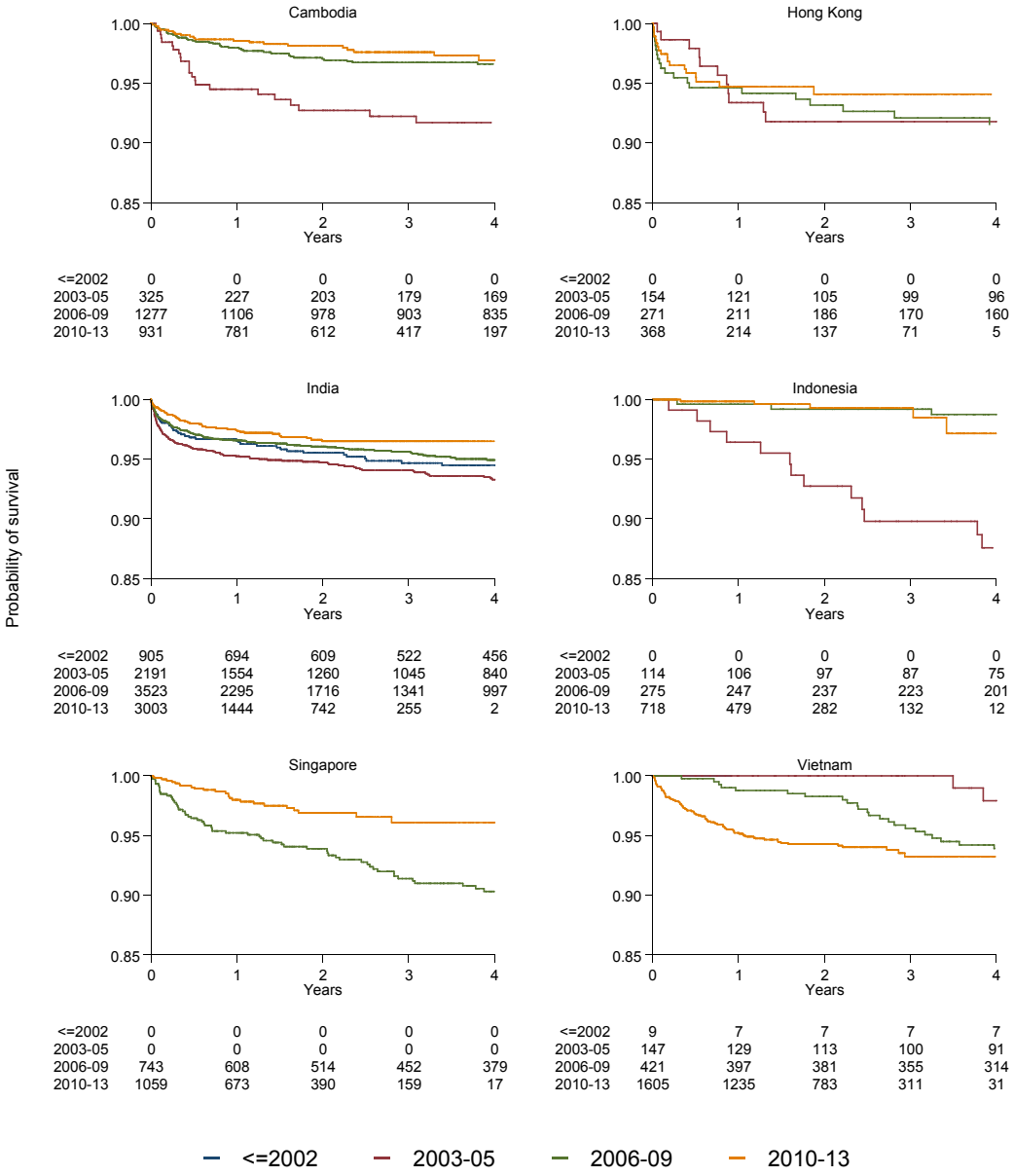
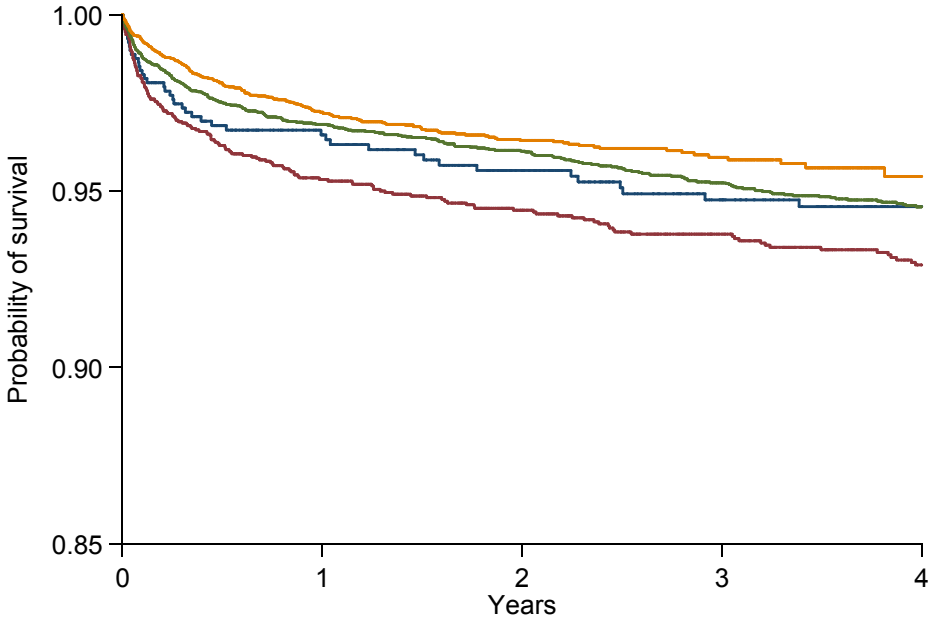


Figure 14.Mortality on first ART for all countries by time period.



<=2002	914	701	616	529	463
2003-05	2931	2137	1778	1510	1271
2006-09	6510	4864	4012	3444	2886
2010-13	7689	4831	2947	1346	264

Figure 15.First ART durability (time to 2nd ART) for each country by time period.

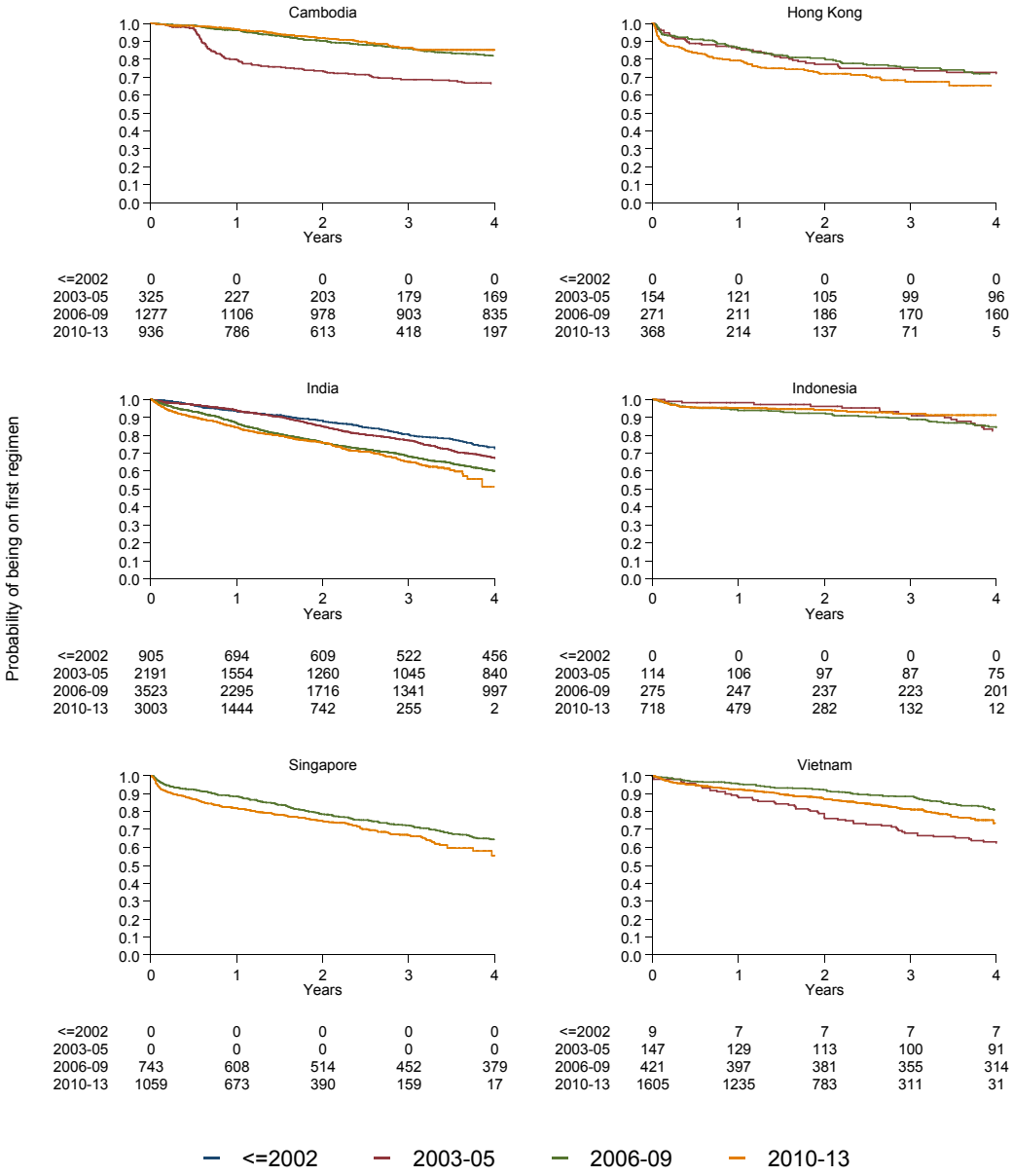
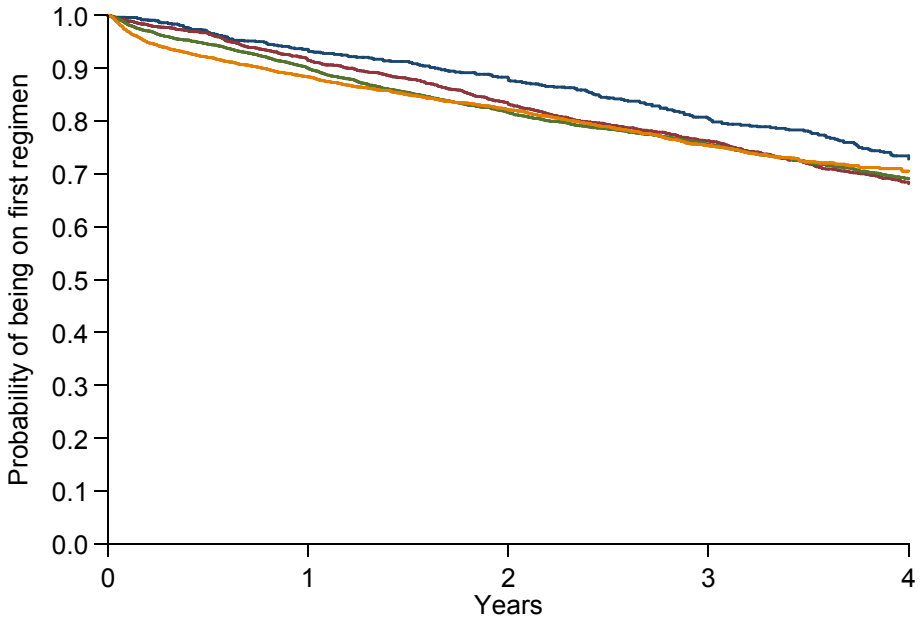


Figure 16.First ART durability (time to 2nd ART) for all countries by time period.



<=2002	914	701	616	529	463
2003-05	2931	2137	1778	1510	1271
2006-09	6510	4864	4012	3444	2886
2010-13	7689	4831	2947	1346	264

Table 3.Risk factors for time to first switch for all countries.

	Number of events	Patient-years	Rate per 100 patient-years	Univariate			Multivariate		
				HR	95% CI	p	HR	95% CI	p
Total	5034	50943.3	9.88						
Year of ART initiation						<0.001			**<0.001**
≤2002	492	4308.9	11.42	1			1		
2003-2005	1164	11627.5	10.01	1.24	(1.11, 1.39)	<0.001	**1.33**	**(1.18, 1.49)**	**<0.001**
2006-2009	2070	22227.0	9.31	1.49	(1.33, 1.67)	<0.001	**1.69**	**(1.51, 1.90)**	**<0.001**
2010-2013	1308	12779.9	10.23	1.73	(1.53, 1.96)	<0.001	**2.11**	**(1.85, 2.40)**	**<0.001**
Age at ART initiation (years)						0.005			0.122
≤30	1406	15746.7	8.93	1			1		
31-40	2288	22573.2	10.14	1.09	(1.02, 1.17)	0.010	1.06	(0.99, 1.14)	0.080
41-50	907	8625.8	10.51	1.13	(1.04, 1.23)	0.004	1.07	(0.98, 1.17)	0.150
51+	433	3997.6	10.83	1.12	(1.00, 1.25)	0.057	1.08	(0.96, 1.21)	0.208
Sex									
Male	3691	34609.3	10.66	1			1		
Female	1343	16334.0	8.22	0.91	(0.86, 0.97)	0.005	**1.12**	**(1.04, 1.20)**	**0.001**
Mode of HIV Exposure						0.730			0.292
Heterosexual	4156	42060.7	9.88	1			1		
Homosexual	311	2624.2	11.85	1.07	(0.93, 1.23)	0.321	1.12	(0.97, 1.29)	0.127
Injecting drug use	239	3015.7	7.93	0.99	(0.85, 1.15)	0.902	0.96	(0.80, 1.14)	0.642
Other/unknown	328	3242.7	10.12	0.98	(0.87, 1.10)	0.700	0.95	(0.85, 1.07)	0.403
Pre-ART viral load (copies/mL)									
≤100,000	366	3777.5	9.69	1			1		
>100,000	473	4430.5	10.68	1.09	(0.95, 1.25)	0.241	0.99	(0.86, 1.14)	0.917
Missing	4195	42735.4	9.82	-			-		

Pre-ART CD4 (cells/µL)						<0.001			**<0.001**
≤50	1018	10550.6	9.65	1			1		
51-100	716	7090.7	10.10	0.91	(0.82, 1.00)	0.048	**0.89**	**(0.81, 0.98)**	**0.022**
101-200	1162	13148.1	8.84	0.77	(0.71, 0.84)	<0.001	**0.75**	**(0.69, 0.82)**	**<0.001**
201+	981	11888.0	8.25	0.73	(0.66, 0.79)	<0.001	**0.68**	**(0.61, 0.74)**	**<0.001**
Missing	1157	8265.9	14.00	-			-		
First ART						<0.001			**<0.001**
NRTI+NNRTI	4712	49217.0	9.57	1			1		
NRTI+PI	283	1587.8	17.82	1.74	(1.53, 1.97)	<0.001	**1.64**	**(1.44, 1.86)**	**<0.001**
Other	39	138.6	28.14	3.16	(2.30, 4.35)	<0.001	**2.98**	**(2.16, 4.10)**	**<0.001**
Previous mono/duo									
No	4667	48780.8	9.57	1			1		
Yes	367	2162.5	16.97	1.71	(1.53, 1.90)	<0.001	**1.78**	**(1.59, 1.99)**	**<0.001**
HBV infection									
Negative	1367	18908.3	7.23	1			1		
Positive	157	2161.8	7.26	1.08	(0.91, 1.27)	0.393	1.06	(0.90, 1.26)	0.467
Not tested	3510	29873.2	11.75	-			-		
HCV infection									
Negative	1948	22980.6	8.48	1			1		
Positive	313	3895.5	8.03	0.99	(0.86, 1.13)	0.879	0.97	(0.83, 1.14)	0.709
Not tested	2773	24067.3	11.52	-			-		

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

6. Second ART

- Second regimen NRTI combination
- Second regimen PI
- Mortality on second regimen
- Durability of second regimen
- Risk factors associated with switch to third regimen

6.1 Methods

First combination ART was defined as the first triple combination. Switch to second and third ART was considered to be a change of drug class or a change of two or more drugs. The proportions of patients starting an antiretroviral/antiretroviral combination by period are presented in Figure 17 to Figure 20. Mortality on second regimen and durability of the second regimen were evaluated using Kaplan-Meier curves (Figure 21 to Figure 24). Risk factors for treatment switch were assessed using Cox regression models stratified by site. The multivariate model is adjusted for all variables shown (Table 4).

6.2 Summary of results

A total of 5,034 patients initiated a second ART regimen. Use of d4T declined after 2003-05 coinciding with an increase in TDF and ABC use. Second regimen use of TDF in Cambodia remains negligible. Non-use of a PI in the second regimen is very common in all countries although overall use of ATV and LPV is increasing.

The country-specific time to event analyses were limited by low patient numbers. Nevertheless, mortality rates were generally highest in earlier time periods. Time to second treatment switch was quickest in higher income countries (Hong Kong and Singapore) and India. Significant risk factors associated with second treatment modification included earlier period of ART initiation, younger age, mode of HIV exposure other than unknown/other, low baseline CD4 cell count, second regimen not containing a PI, and previous mono/duo exposure.

Figure 17.Second regimen NRTI combination for each country by time period.

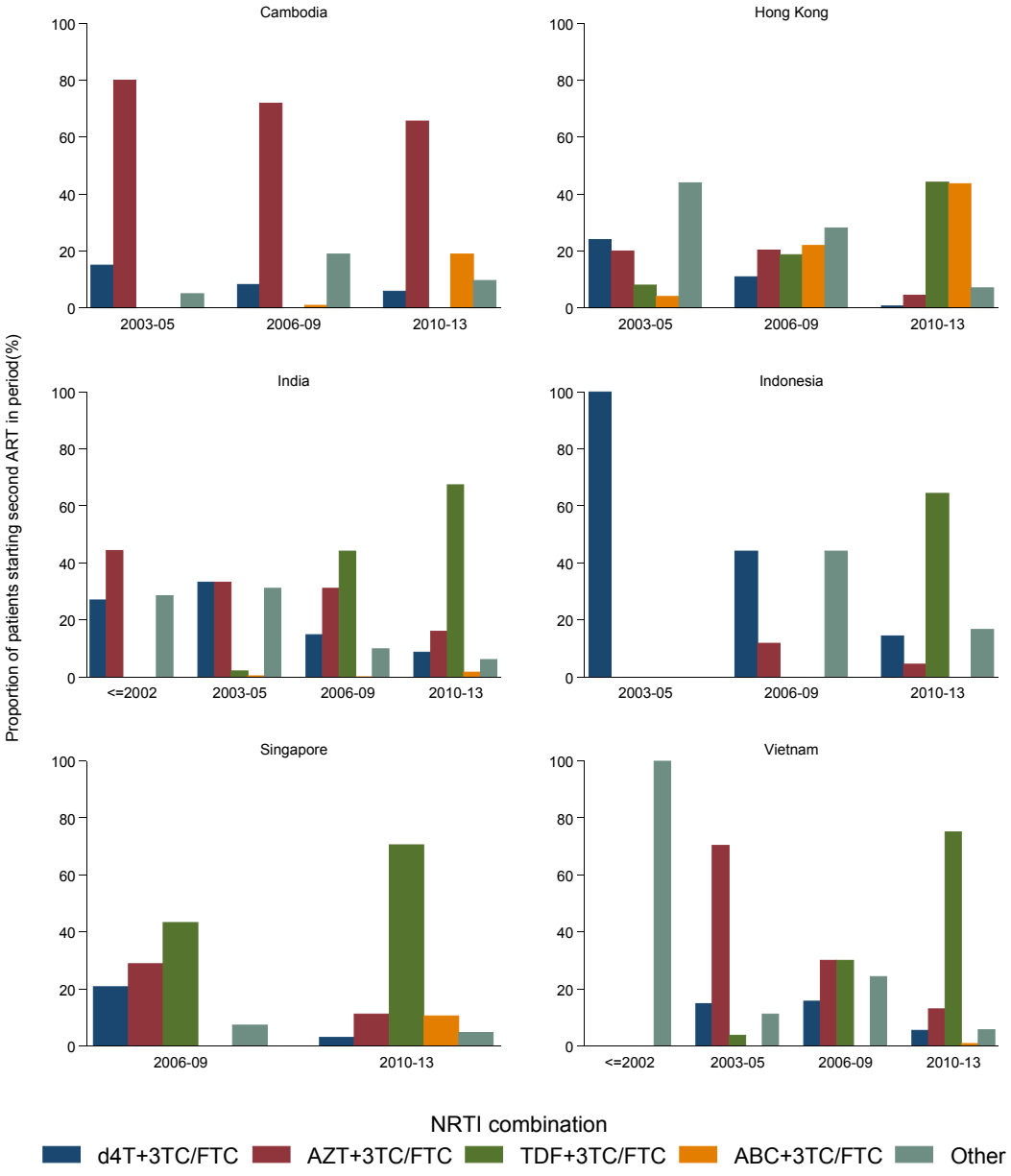


Figure 18.Second regimen NRTI combination for all countriesby time period.

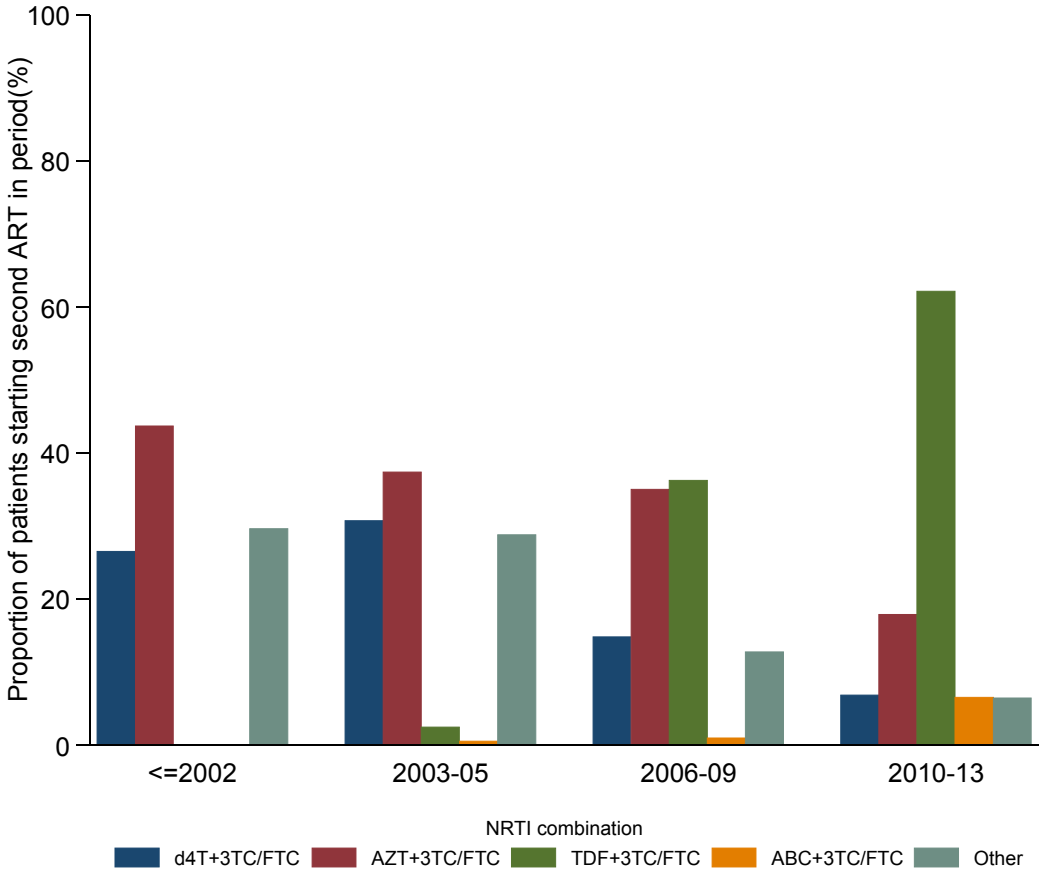


Figure 19.Second regimen PI for each country by time period.

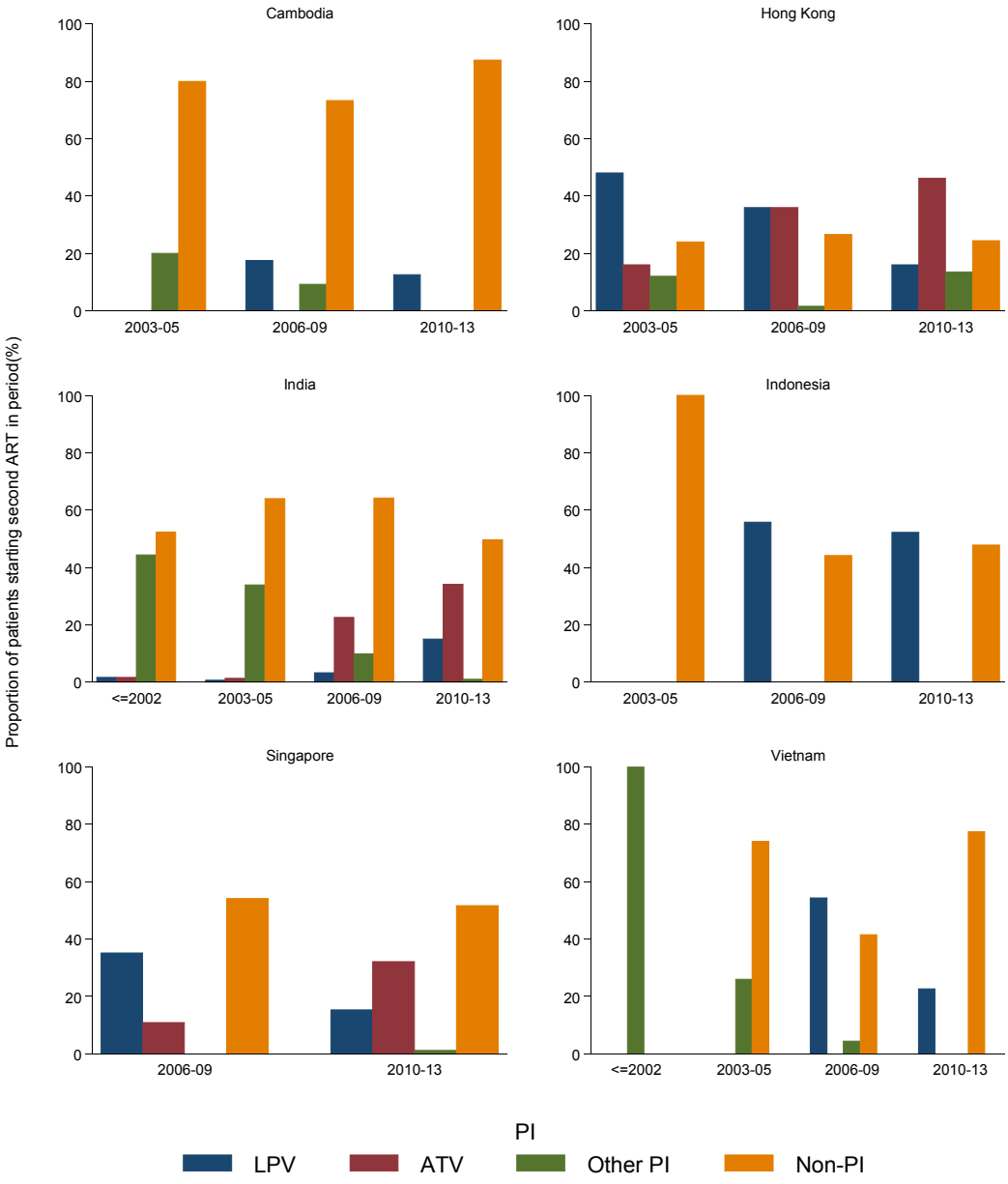


Figure 20.Second regimen PI for all countriesby time period.

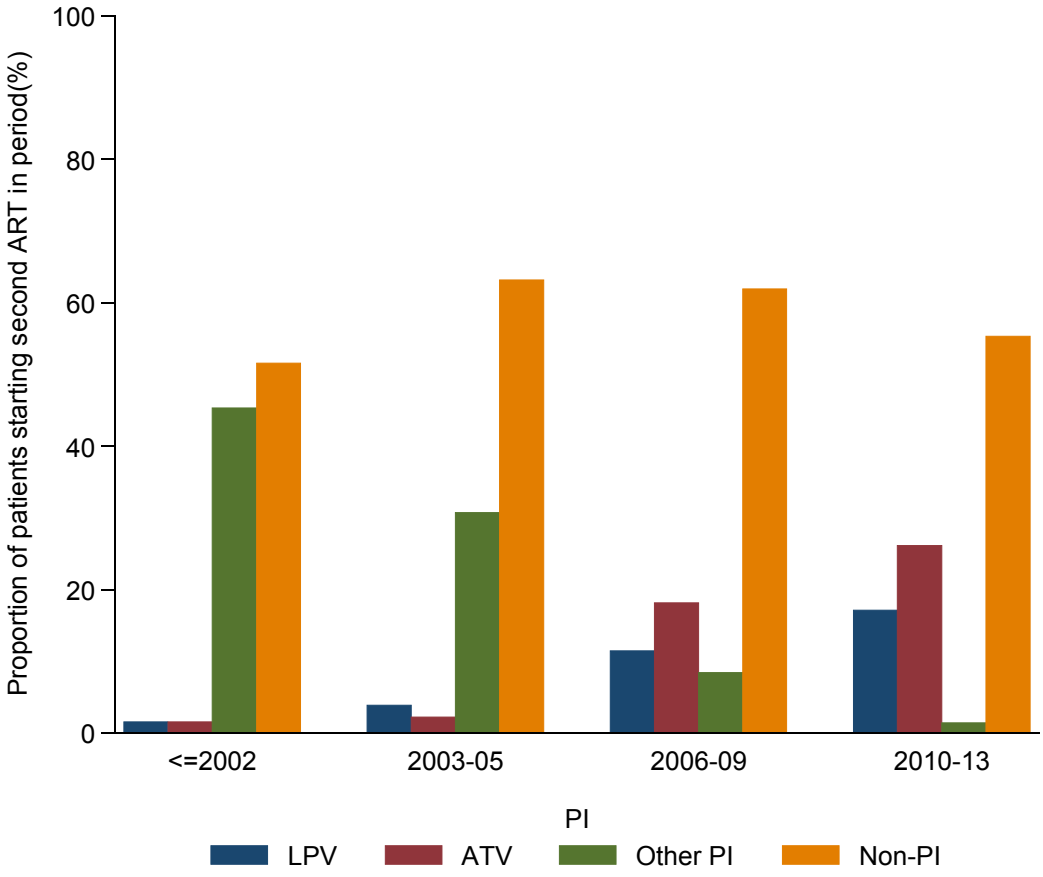


Figure 21.Mortality on second ART for each country by time period.

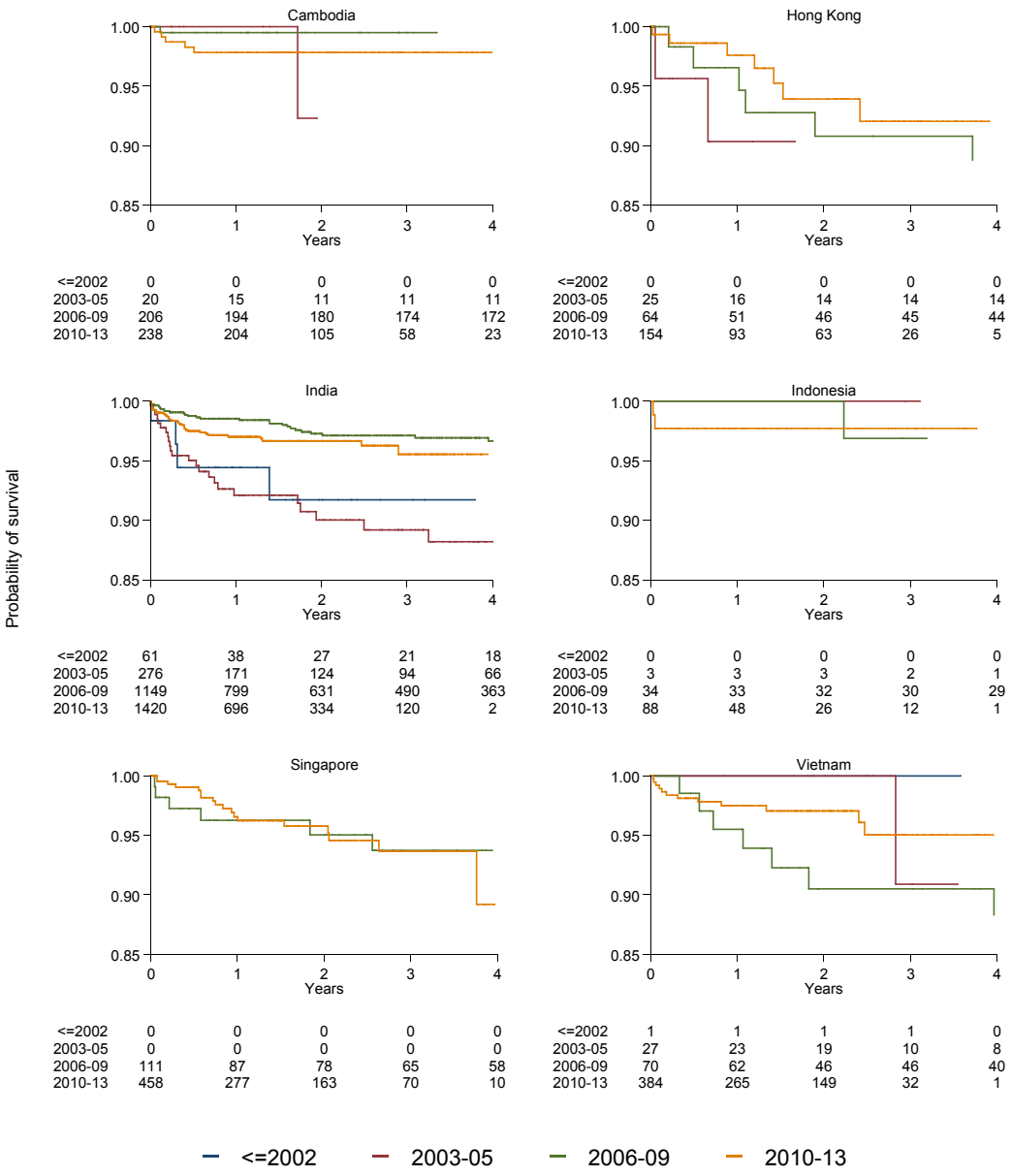
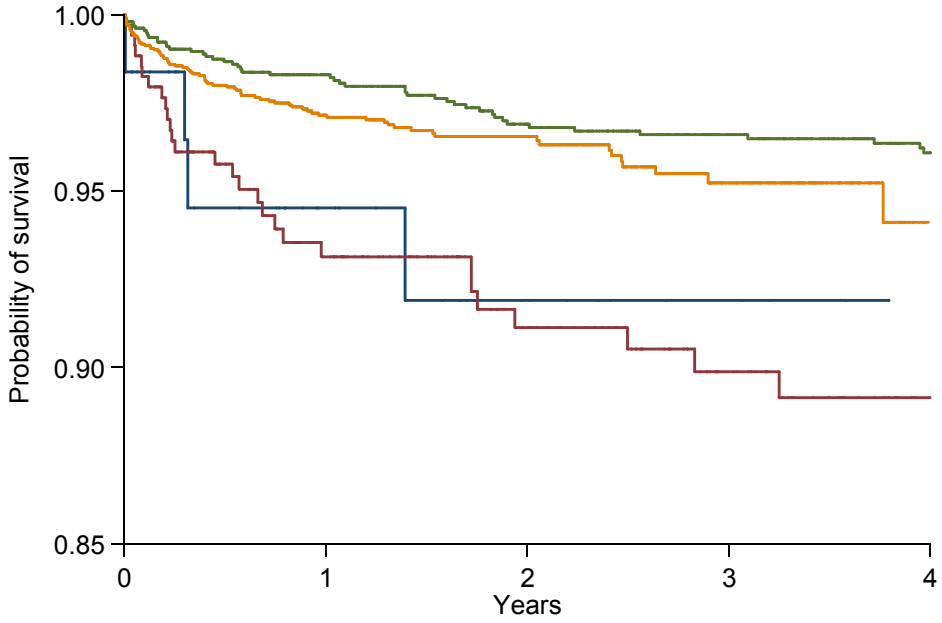


Figure 22.Mortality on second ART for all countries by time period.



<=2002	62	39	28	22	18
2003-05	351	228	171	131	100
2006-09	1634	1226	1013	850	706
2010-13	2742	1583	840	318	42

Figure 23.Second ART durability (time to 3rd ART) for each country by time period.

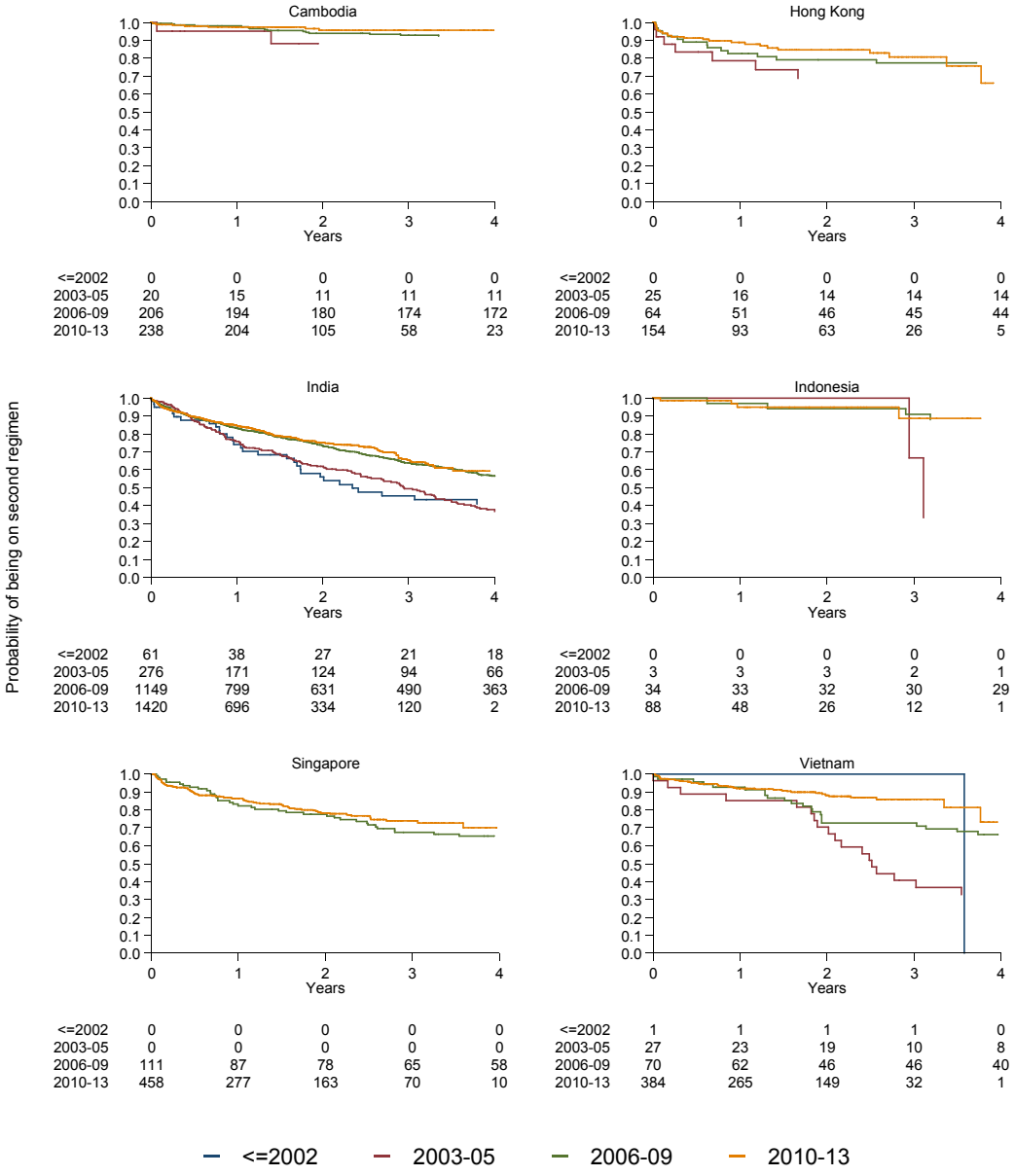
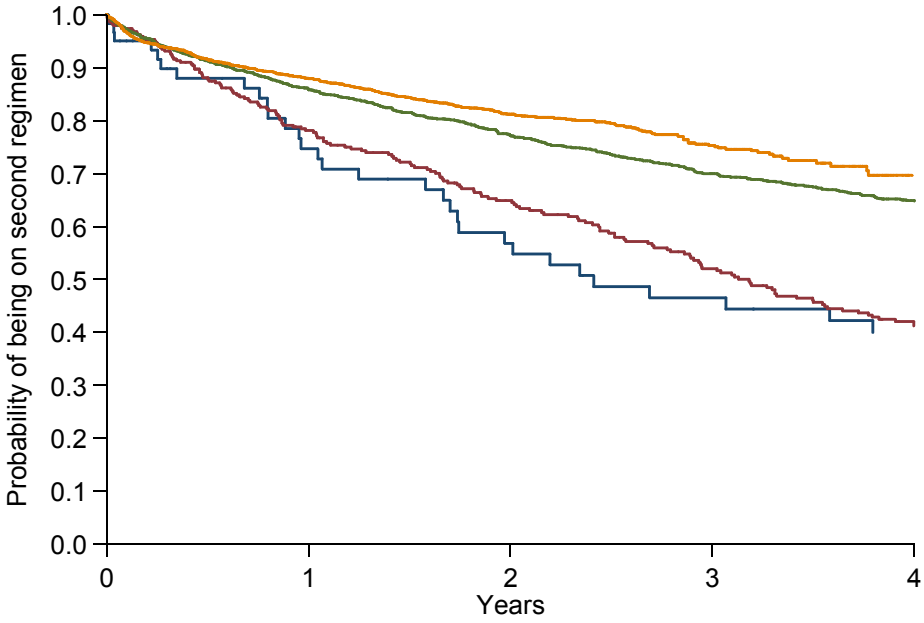


Figure 24.Second ART durability (time to 3rd ART) for all countries by time period.



<=2002	62	39	28	22	18
2003-05	351	228	171	131	100
2006-09	1634	1226	1013	850	706
2010-13	2742	1583	840	318	42

Table 4.Risk factors for time to second switch for all countries.

	Number of events	Patient-years	Rate per 100 patient-years	Univariate			Multivariate		
				HR	95% CI	p	HR	95% CI	p
Total	1241	10500.2	11.82						
Year of second ART initiation						<0.001			**0.001**
≤2002	43	177.7	24.19	1			1		
2003-2005	204	1037.3	19.67	1.00	(0.72, 1.39)	0.988	0.89	(0.64, 1.25)	0.507
2006-2009	563	5299.2	10.62	0.61	(0.44, 0.84)	0.002	**0.68**	**(0.49, 0.94)**	**0.020**
2010-2013	431	3986.0	10.81	0.55	(0.40, 0.77)	<0.001	**0.66**	**(0.47, 0.92)**	**0.014**
Age at second ART initiation (years)						0.002			**0.034**
≤30	175	1367.2	12.80	1			1		
31-40	613	5033.3	12.18	0.92	(0.78, 1.09)	0.361	0.97	(0.82, 1.16)	0.775
41-50	323	2781.3	11.61	0.83	(0.69, 1.01)	0.057	0.89	(0.73, 1.08)	0.244
51+	130	1318.4	9.86	0.71	(0.57, 0.90)	0.005	0.80	(0.63, 1.02)	0.078
Sex									
Male	930	7544.6	12.33	1			1		
Female	311	2955.6	10.52	0.95	(0.83, 1.08)	0.422	1.01	(0.88, 1.16)	0.858
Mode of HIV Exposure						0.012			**0.014**
Heterosexual	1070	8614.1	12.42	1			1		
Homosexual	63	588.6	10.70	1.01	(0.75, 1.36)	0.972	1.04	(0.76, 1.41)	0.817
Injecting drug use	43	566.5	7.59	0.87	(0.61, 1.23)	0.419	0.82	(0.56, 1.22)	0.331
Other/unknown	65	731.0	8.89	0.66	(0.51, 0.85)	0.001	**0.67**	**(0.52, 0.86)**	**0.002**
Pre-second ART viral load (copies/mL)									
≤100,000	197	2426.8	8.12	1			1		
>100,000	81	745.4	10.87	1.34	(1.03, 1.74)	0.029	1.14	(0.87, 1.50)	0.342
Missing	963	7328.0	13.14	-			-		

Pre-second ART CD4 (cells/µL)						**<0.001**			**<0.001**
≤50	188	1234.6	15.23	1			1		
51-100	146	1100.2	13.27	0.82	(0.66, 1.02)	0.073	0.83	(0.67, 1.04)	0.107
101-200	239	2209.7	10.82	0.75	(0.61, 0.90)	0.003	**0.70**	**(0.57, 0.86)**	**0.001**
201+	452	4932.9	9.16	0.58	(0.48, 0.69)	<0.001	**0.55**	**(0.45, 0.66)**	**<0.001**
Missing	216	1022.8	21.12	-			-		
Second ART						<0.001			**<0.001**
NRTI+PI	425	3900.7	10.90	1			1		
NRTI+NNRTI	756	6277.6	12.04	1.24	(1.10, 1.41)	<0.001	**1.45**	**(1.27, 1.66)**	**<0.001**
Other	60	321.9	18.64	1.73	(1.32, 2.27)	<0.001	**2.17**	**(1.63, 2.88)**	**<0.001**
Previous mono/duo									
No	1083	9718.8	11.14	1			1		
Yes	158	781.4	20.22	1.54	(1.30, 1.82)	<0.001	**1.48**	**(1.24, 1.76)**	**<0.001**
HBV infection									
Negative	227	3476.2	6.53	1			1		
Positive	19	454.0	4.18	0.74	(0.46, 1.19)	0.216	0.69	(0.43, 1.11)	0.122
Not tested	995	6569.9	15.14	-			-		
HCV infection									
Negative	402	4580.0	8.78	1			1		
Positive	59	745.2	7.92	0.97	(0.72, 1.32)	0.867	1.05	(0.75, 1.47)	0.781
Not tested	780	5175.0	15.07	-			-		

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

7. Rates of CD4 and viral load testing

- Rates of CD4 testing.
- Rates of viral load testing.

7.1 Methods

Rates of CD4 testing after ART initiation are presented according to each follow-up time period, in Figure 25 and Figure 26. CD4 tests prior to ART initiation were excluded. Rates and their 95% CI were plotted per person year of follow-up (pys).

Rates of viral load (VL) testing after ART initiation are presented according to each follow-up time period, in Figure 27 and Figure 28. VL tests prior to ART initiation were excluded. Rates and their 95% CI were plotted per person year of follow-up (pys).

7.2 Summary of results

The crude rate of CD4 testing for all countries and all time periods was 1.8 pys with 95% CI (1.82-1.84). Hong Kong and Singapore show rates above 2.0 pys for all time periods. Cambodia and India show increasing rates of CD4 testing from approximately 1.0 pys in the period 2003-2005 to approximately 2.0 pys in the 2006-2009 time period. Rates in Vietnam were approaching 2.0 pys in 2010-2013. Indonesia has had stable CD4 testing rates at approximately 1.0 pys for all time periods. Overall, a sharp increase was seen between 2003-2005 and 2006-2009 time periods.

The crude rate of VL testing for all countries and all time periods was 0.6 pys with 95% CI (0.61-0.62). Hong Kong showed rates above 1.0 pys for all time periods, while Singapore showed a VL testing increase between 2006-2009 and 2010-2013. All other countries have rates at approximately 1.0 pys or less for all time periods. Overall in all countries combined, rates of VL testing have increased across time periods.

Figure 25.Rates of CD4 testing for each country by time period.

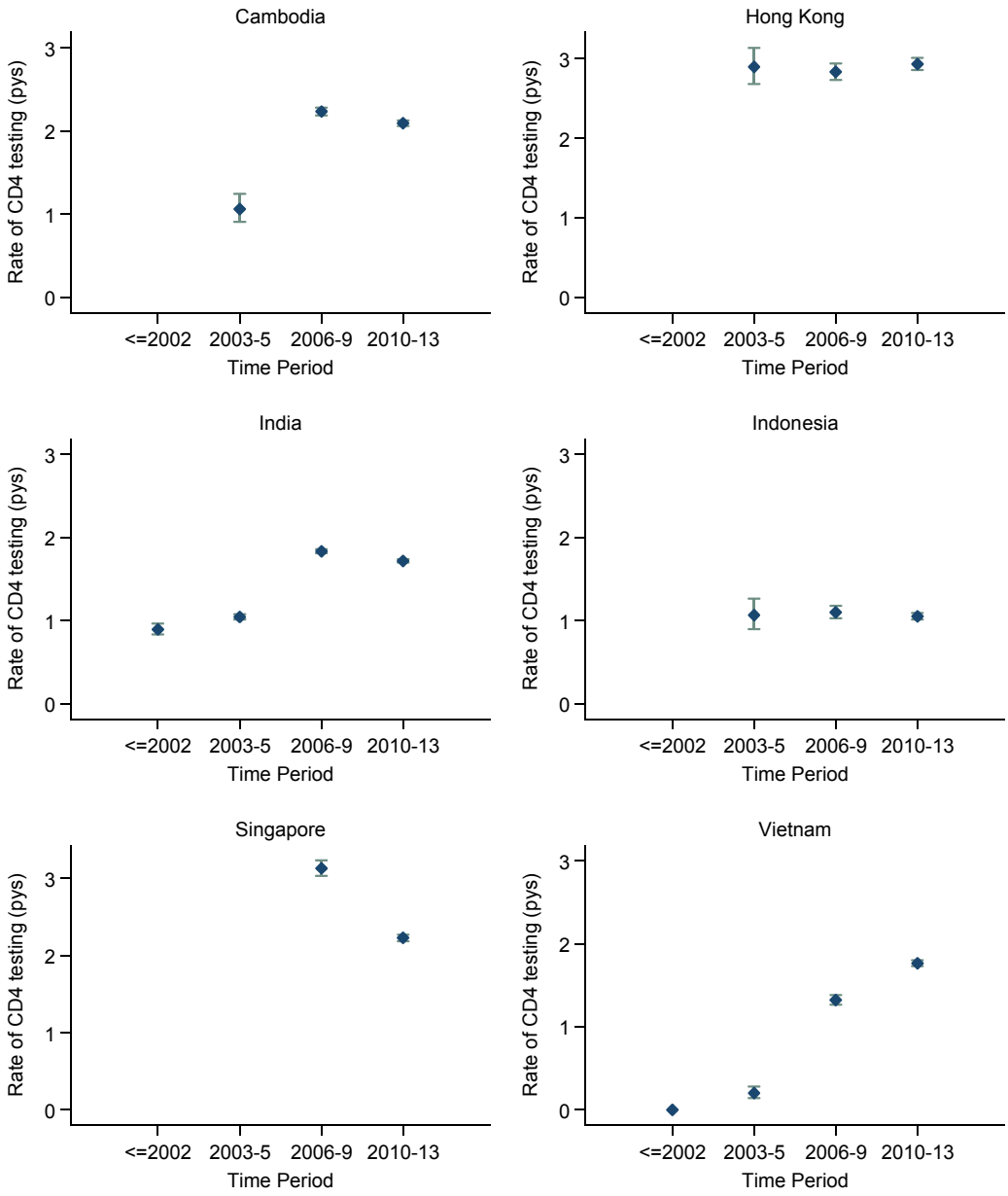


Figure 26.Rates of CD4 testing for all countries by time period.

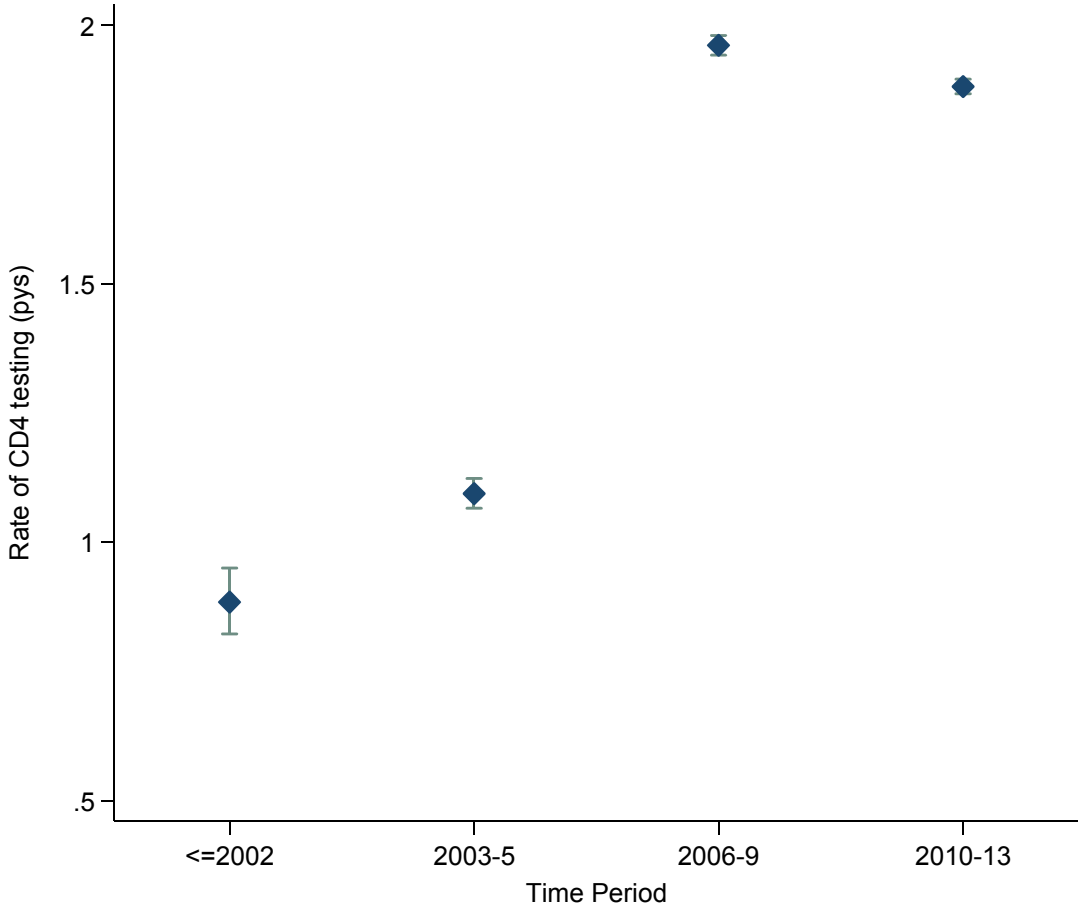


Figure 27.Rates of HIV viral load testing for each country by time period.

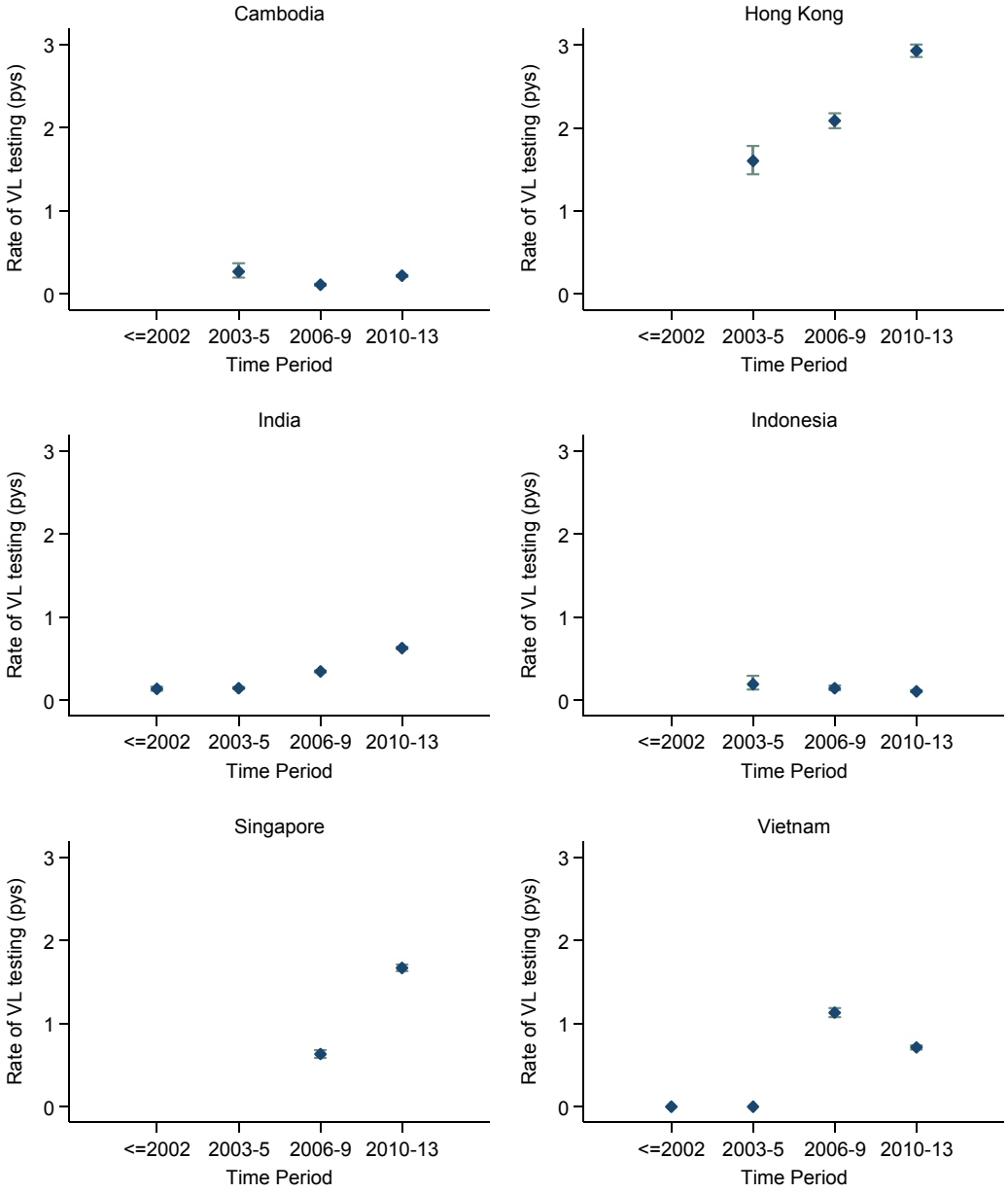
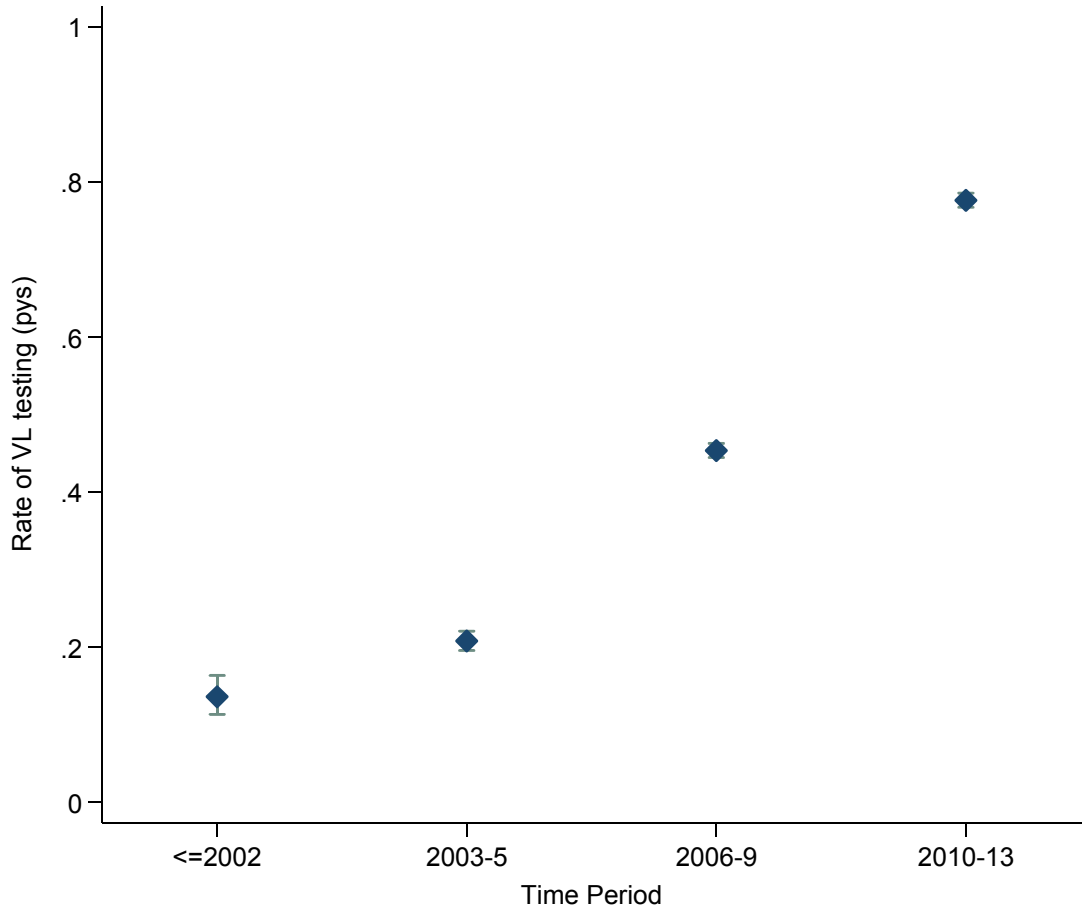


Figure 28.Rates of HIV viral load testing for all countries by time period.



8. CD4 response from ART initiation

- CD4 changes from ART initiation.
- Factors associated with CD4 increase at 12 months after ART initiation.

8.1 Methods

Patients with a CD4 count within 6 months prior to ART initiation and at least one CD4 count after ART initiation were included. Changes in CD4 count was defined as the difference between CD4 count at a given time period and the pre-treatment value. Positive CD4 changes indicate increases in CD4 count from pre-treatment levels. Mean CD4 changes were graphically displayed according to year of ART initiation and time from ART start, in Figure 29 and Figure 30. Factors associated with mean CD4 change/increase at 12 months from ART initiation were analysed using linear regression adjusted for site. Only patients with a CD4 count at 12 months from ART initiation were included in the regression models. The multivariate model is adjusted for all variables shown in Table 5.

8.2 Summary of results

The average increase in CD4 count at 12 months after ART initiation was 181 cells/μL. In the multivariate analysis, year of ART initiation was not significantly associated with mean CD4 increase at 12 months. However age, sex, HIV mode of exposure, pre-treatment viral load and CD4 count, prior mono/duo therapy and hepatitis C co-infection were significant predictors of CD4 increase, adjusting for all other covariates.

Figure 29.CD4 changes from ART initiation for each country by time period.

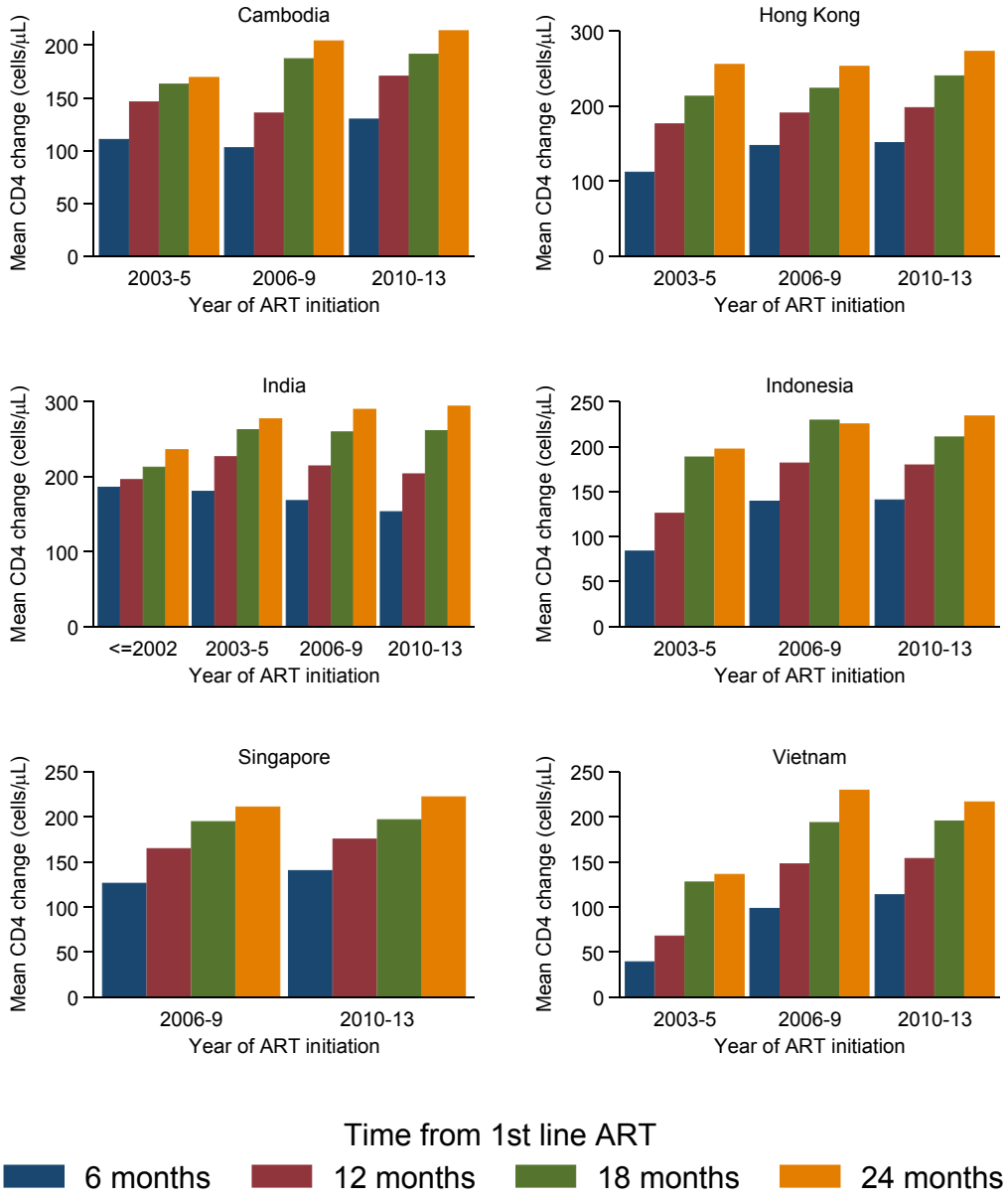


Figure 30.CD4 changes from ART initiation for all countries by time period.

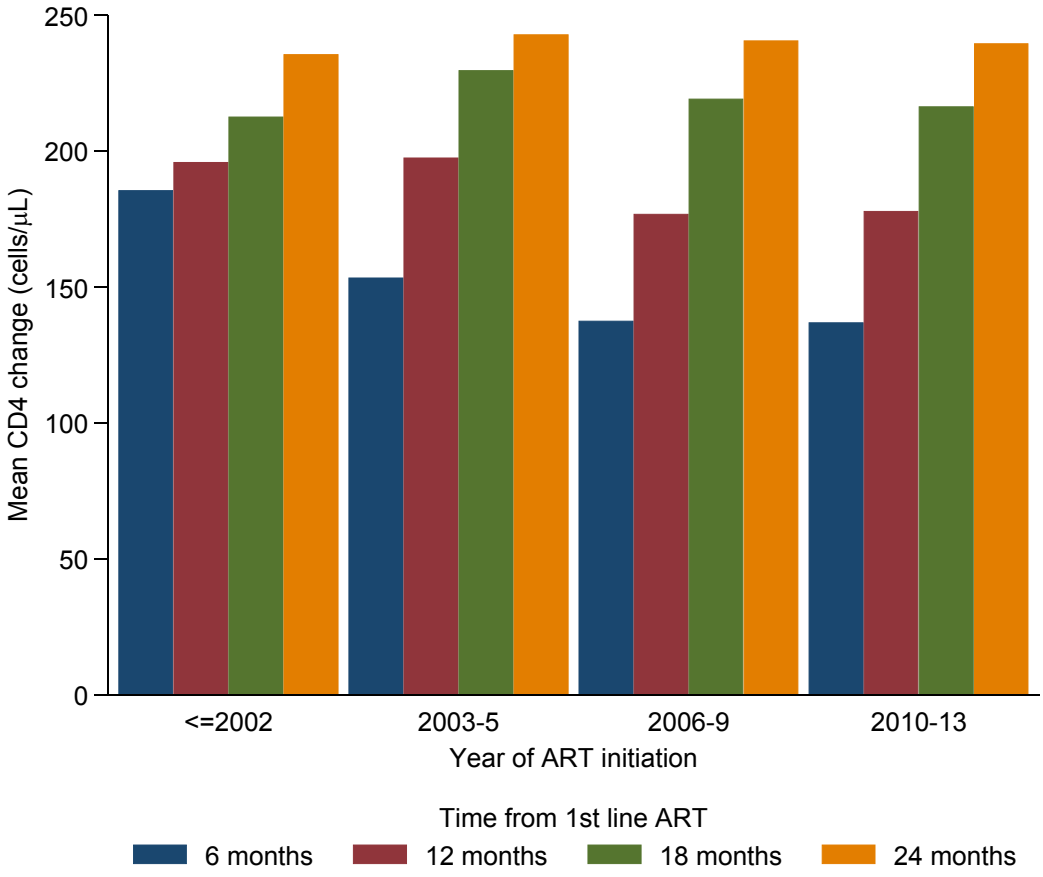


Table 5.CD4 increase at 12 months after ART initiation.

	Number of patients	Mean CD4 increase	Univariate			Multivariate		
			Diff	95% CI	p	Diff	95% CI	p
Total	9111	181						
Year of ART initiation					0.089			0.084
≤2002	271	196	-20	(-42, 2)	0.072	-16	(-38, 6)	0.167
2003-2005	1280	197	Ref			Ref		
2006-2009	3634	177	-7	(-18, 4)	0.212	-9	(-20, 2)	0.097
2010-2013	3926	178	2	(-9, 13)	0.738	3	(-9, 15)	0.609
Age at ART initiation (years)					<0.001			**<0.001**
≤30	2454	188	Ref			Ref		
31-40	3987	184	-10	(-18, -1)	0.025	-8	(-17, 0)	0.060
41-50	1754	170	-25	(-36, -15)	<0.001	**-25**	**(-35, -14)**	**<0.001**
51+	916	165	-28	(-41, -15)	<0.001	**-28**	**(-42, -15)**	**<0.001**
Sex								
Male	6105	177	Ref			Ref		
Female	3006	189	20	(12, 27)	<0.001	**16**	**(8, 24)**	**<0.001**
Mode of HIV Exposure					<0.001			**0.040**
Heterosexual contact	7289	183	Ref			Ref		
Homosexual contact	708	187	15	(0, 31)	0.048	12	(-3, 28)	0.125
Injecting drug use	493	128	-37	(-54, -20)	<0.001	**-20**	**(-40, 0)**	**0.050**
Other/unknown	621	192	11	(-3, 25)	0.129	10	(-4, 24)	0.166
Pre-ART viral load (copies/mL)								
≤100000	1009	165	Ref			Ref		
>100000	1223	211	46	(32, 60)	<0.001	**43**	**(29, 57)**	**<0.001**
Missing	6879	178						

Pre-ART CD4 (cells/μL)					0.006			**0.001**
≤50	2344	175	Ref			Ref		
51-100	1404	189	4	(-7, 15)	0.500	3	(-8, 15)	0.543
101-200	2479	192	3	(-7, 13)	0.575	1	(-9, 11)	0.868
201+	2884	172	-13	(-22, -3)	0.007	**-16**	**(-26, -7)**	**0.001**
First ART regimen					0.084			0.234
NRTI+NNRTI	8738	181	Ref			Ref		
NRTI+PI	341	191	-1	(-19, 18)	0.929	6	(-13, 24)	0.548
Other	32	109	-66	(-124, -8)	0.026	-46	(-104, 11)	0.115
Previous mono/duo exposure								
No	8761	182	Ref			Ref		
Yes	350	147	-53	(-71, -35)	<0.001	**-47**	**(-65, -29)**	**<0.001**
Hepatitis B co-infection								
Negative	4199	166	Ref			Ref		
Positive	472	148	-16	(-32, 0)	0.052	-14	(-30, 1)	0.074
Not tested	4440	198						
Hepatitis C co-infection								
Negative	4858	170	Ref			Ref		
Positive	757	135	-30	(-44, -16)	<0.001	**-17**	**(-34, -0)**	**0.045**
Not tested	3496	205						

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

9. Viral load response from ART initiation

- VL <400 copies/mL from ART initiation.
- Factors associated with VL <400 copies/mL at 12 months after ART initiation.

9.1 Methods

Patients with at least one viral load (VL) test after ART initiation were included. The proportion of VL <400 copies/ml was calculated as a fraction of patients with VL <400 copies/ml out of those who had VL testing for each time period, in Figure 31 and Figure 32. Factors associated with VL <400 copies/ml at 12 months after ART initiation was analysed using logistic regression with site modelled as a random effect. Only patients with a VL test at 12 months after ART initiation were included in the regression analysis. The multivariate model is adjusted for all variables shown in Table 6.

9.2 Summary of results

The number of patients with VL testing in the early periods of ART in lower income countries were relatively small compared to higher income countries. Therefore the small proportions of patients with VL <400 copies/ml seen in these countries reflect the small number of patients tested, and most likely targeted testing of those most at risk of treatment failure, rather than suboptimal treatment response. It is important to note that these graphical displays (Figure 31and Figure 32) illustrate available data from the sites and should not be overly interpreted due to biases associated with targeted VL testing within these sites.

Overall, the proportion of patients with VL <400 copies/ml increased for each time period of ART initiation, but have remained steady at each treatment duration interval. The regression model indicates that patients starting ART in later years were more likely to reach VL <400 copies/ml at 12 months. Being female was also associated with favourable VL outcome.

Figure 31.VL <400 copies/mL from ART initiation for each country by time period.

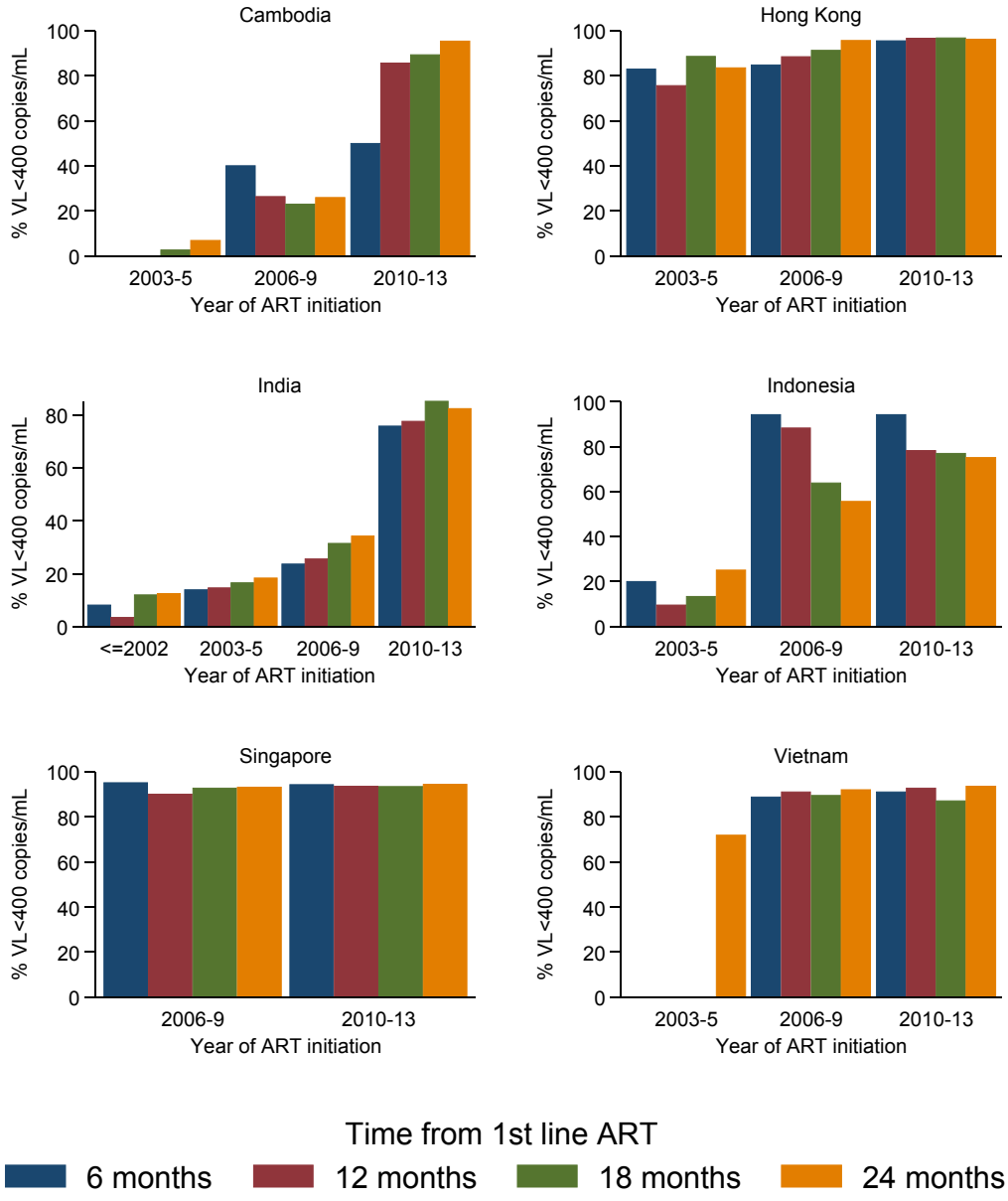


Figure 32.VL <400 copies/mL from ART initiation for all countries by time period.

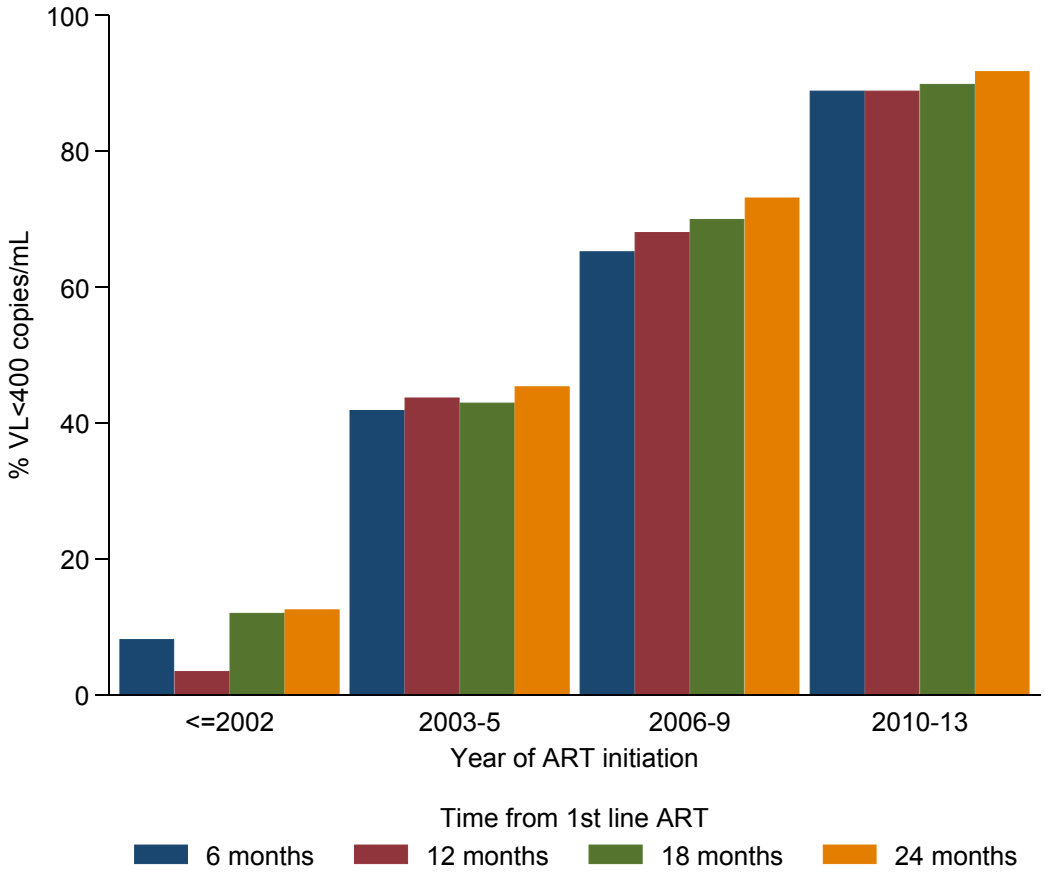


Table 6.VL <400 copies/mL at 12 months after ART initiation.

	Number of patients	Number with VL <400 copies/mL	Univariate			Multivariate		
			OR	95% CI	p	OR	95% CI	p
Total	3152	2457						
Year of ART initiation					<0.001			**<0.001**
≤2002	29	1	0.2	(0.0, 1.6)	0.134	0.3	(0.0, 2.3)	0.234
2003-2005	229	100	1			1		
2006-2009	1032	702	3.1	(2.1, 4.5)	<0.001	**3.6**	**(2.3, 5.5)**	**<0.001**
2010-2013	1862	1654	15.9	(10.6, 23.8)	<0.001	**20.4**	**(13.0, 32.2)**	**<0.001**
Age at ART initiation (years)					0.561			0.331
≤30	793	614	1			1		
31-40	1285	958	1.1	(0.8, 1.4)	0.568	1.2	(0.9, 1.6)	0.209
41-50	661	536	1.3	(0.9, 1.7)	0.121	1.3	(0.9, 1.8)	0.134
51+	413	349	1.0	(0.7, 1.4)	0.799	1.1	(0.7, 1.7)	0.569
Sex								
Male	2346	1844	1			1		
Female	806	613	1.5	(1.2, 1.9)	<0.001	**1.5**	**(1.2, 2.0)**	**0.001**
Mode of HIV Exposure					0.005			0.314
Heterosexual contact	2062	1492	1			1		
Homosexual contact	570	531	1.7	(1.1, 2.5)	0.010	1.3	(0.8, 2.0)	0.230
Injecting drug use	235	200	0.6	(0.4, 0.9)	0.027	0.8	(0.4, 1.5)	0.498
Other/unknown	285	234	1.1	(0.8, 1.6)	0.475	1.3	(0.9, 2.0)	0.187
Pre-ART viral load (copies/mL)								
≤100000	800	616	1			1		
>100000	931	713	1.0	(0.8, 1.3)	0.885	0.9	(0.7, 1.2)	0.585
Missing	1421	1128						

Pre-ART CD4 (cells/µL)					0.040			0.632
≤50	744	630	1			1		
51-100	376	308	1.3	(0.9, 1.9)	0.187	1.2	(0.8, 1.8)	0.342
101-200	622	481	1.4	(1.0, 1.9)	0.042	1.3	(0.9, 1.9)	0.132
201+	1192	874	1.3	(1.0, 1.8)	0.058	0.9	(0.6, 1.2)	0.474
Missing	218	164						
First ART regimen					0.001			0.152
NRTI+NNRTI	2892	2268	1			1		
NRTI+PI	237	171	0.5	(0.4, 0.7)	<0.001	0.6	(0.4, 1.0)	0.056
Other	23	18	0.5	(0.2, 1.7)	0.285	0.8	(0.2, 2.7)	0.668
Previous mono/duo exposure								
No	3046	2384	1			1		
Yes	106	73	0.5	(0.3, 0.8)	0.005	1.0	(0.6, 1.9)	0.944
Hepatitis B co-infection								
Negative	1669	1501	1			1		
Positive	157	139	0.9	(0.5, 1.5)	0.589	1.1	(0.6, 2.0)	0.646
Not tested	1326	817						
Hepatitis C co-infection								
Negative	1980	1749	1			1		
Positive	344	299	0.6	(0.4, 0.9)	0.015	1.0	(0.6, 1.7)	0.981
Not tested	828	409						

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

10. CD4 response from start of second ART regimen

- CD4 changes from start of second ART regimen.
- Factors associated with CD4 increase at 12 months from start of second ART regimen.

10.1 Methods

Patients who have switched to second ART regimen with at least one CD4 count within 6 months prior to switch and at least one CD4 count after switch to second ART were included. Second ART regimen was defined as a change of 2 drugs or 1 drug class change due to any reason. Change in CD4 count was defined as the difference between CD4 count at a given time period and the CD4 count prior to switch. Positive CD4 changes indicate increases in CD4 count. Mean CD4 changes were graphically displayed according to year of starting second ART regimen in Figure 33 and Figure 34. Factors associated with mean CD4 change/increase at 12 months from start of second ART were analysed using linear regression adjusted for site. Only patients with a CD4 count at 12 months from the switch date were included in the regression model. The multivariate model is adjusted for all variables shown in Table 7.

10.2 Summary of results

There has been an increase in CD4 count from second ART regimen for all countries across all time periods. In Cambodia, those who switched between 2003-2005 had a drop in the increase of CD4 at 18 months compared to 12 months. Similarly for India, there has been a slight drop in CD4 increase at 18 months for those who switched prior to 2003, and at 24 months for those who switched to second ART between 2003-2005. For Indonesia, a slight drop can be seen at month 18 for those who switched between 2010-2013. Vietnam also shows a drop in CD4 increase at 24 months for 2003-2005. Overall, CD4 has been increasing for all time periods with the exception of those who switched prior 2003, where the average increase are scattered across treatment duration. The multivariate results show that the average increase in CD4 count at 12 months after starting second ART was higher in females, those with higher VL and lower CD4 count and those on regimen other than NRTI+NNRTI . Year of starting second ART was not a statistically significant factor.

Figure 33.CD4 changes from start of second ART regimen for each country by time period.

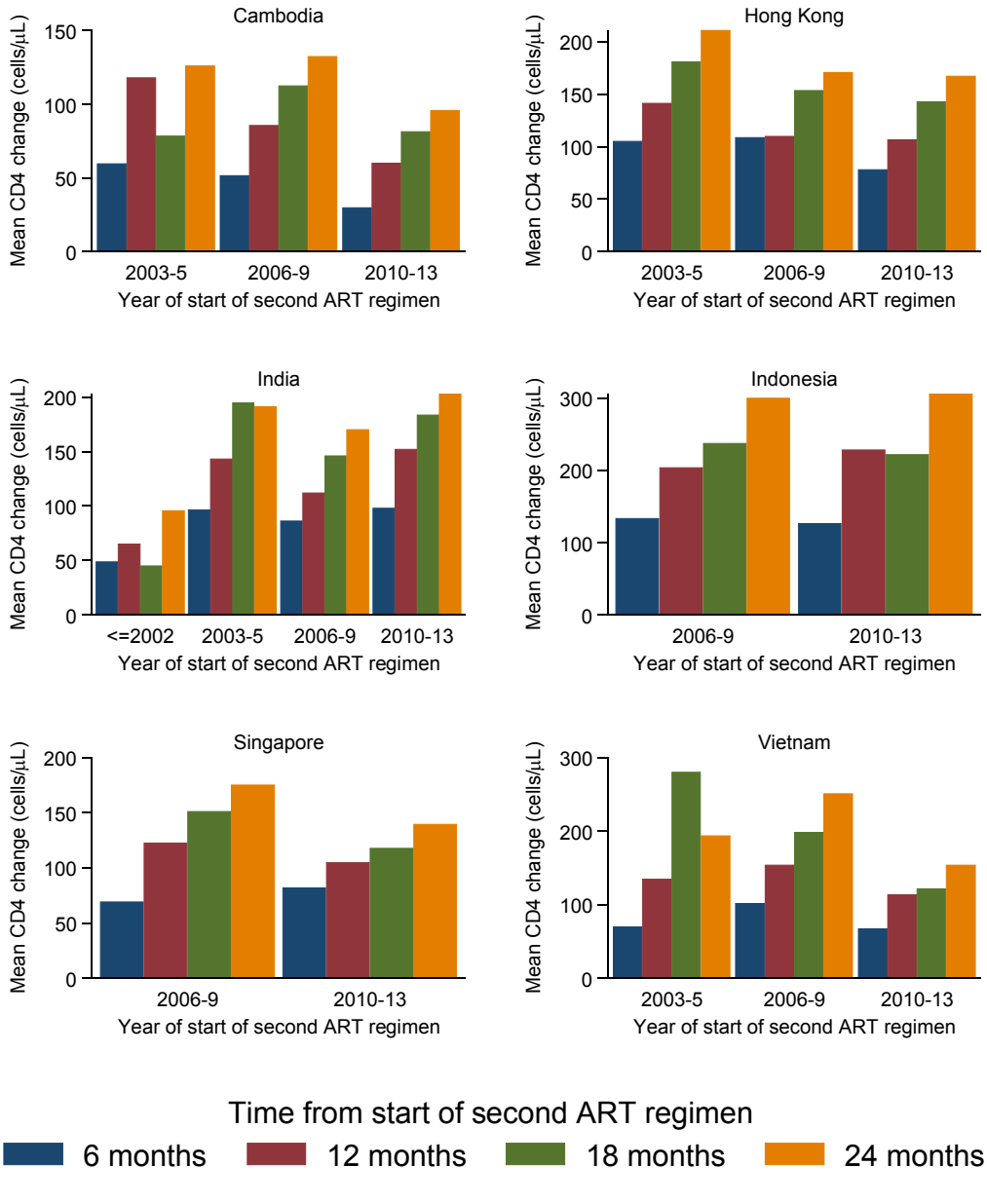


Figure 34.CD4 changes from start of second ART regimen for all countries by time period.

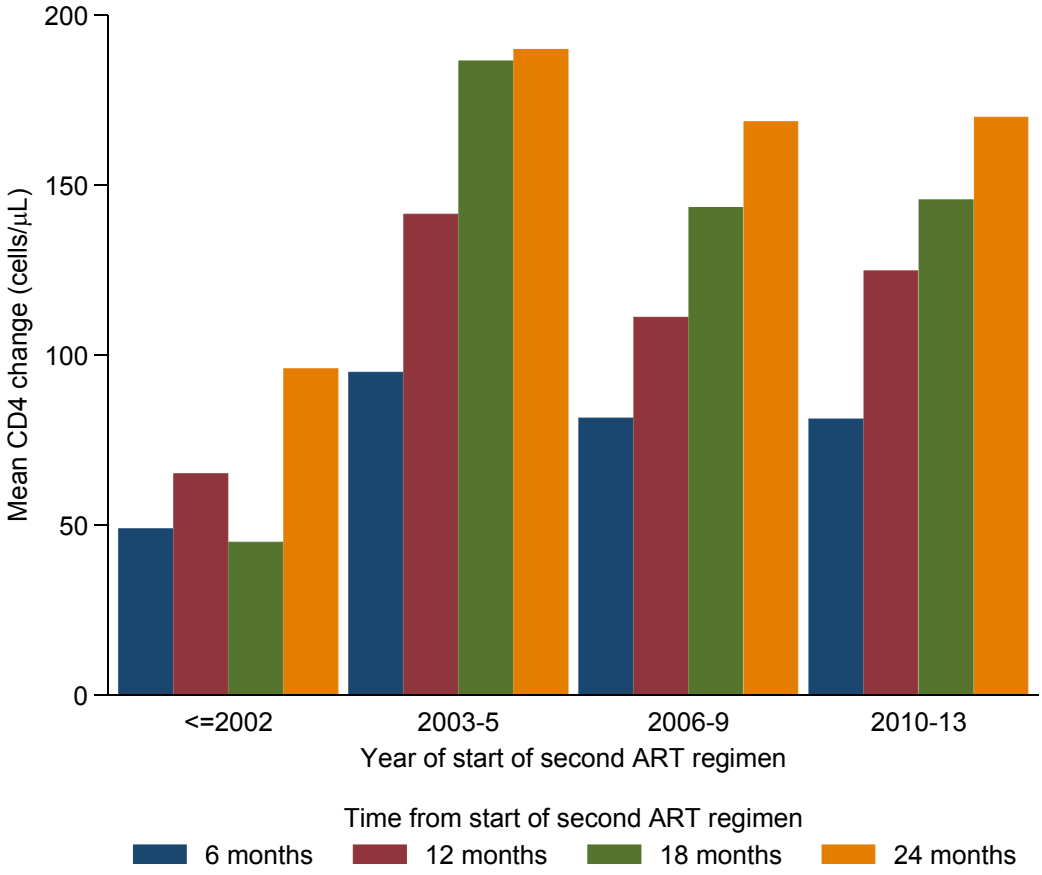


Table 7.CD4 increase at 12 months from start of second ART regimen.

	Number of patients	Mean CD4 increase	Univariate			Multivariate		
			Diff	95% CI	p	Diff	95% CI	p
Total	2456	120						
Year of start of second ART regimen					0.281			0.101
≤2002	32	65	-82	(-172, 8)	0.075	-79	(-167, 9)	0.078
2003-2005	190	141	Ref			Ref		
2006-2009	1027	111	-24	(-62, 13)	0.203	-6	(-43, 32)	0.771
2010-2013	1207	125	-9	(-47, 29)	0.648	8	(-31, 47)	0.677
Age at switch of second ART regimen (years)					0.032			0.057
≤30	391	133	Ref			Ref		
31-40	1160	123	-10	(-38, 18)	0.472	-9	(-37, 18)	0.509
41-50	588	123	-10	(-41, 22)	0.548	-8	(-40, 23)	0.603
51+	317	86	-46	(-83, -9)	0.014	**-41**	**(-78, -5)**	**0.028**
Sex								
Male	1786	119	Ref			Ref		
Female	670	121	7	(-15, 29)	0.536	**23**	**(0, 46)**	**0.048**
Mode of HIV Exposure					0.318			0.343
Heterosexual contact	2007	118	Ref			Ref		
Homosexual contact	174	134	33	(-10, 76)	0.134	40	(-3, 84)	0.069
Injecting drug use	109	107	-26	(-79, 26)	0.325	5	(-54, 64)	0.862
Other/unknown	166	127	9	(-30, 48)	0.653	8	(-30, 46)	0.680
Viral load at start of second ART regimen (copies/mL)								
≤100000	698	105	Ref			Ref		
>100000	226	211	102	(66, 138)	<0.001	**49**	**(13, 86)**	**0.009**
Missing	1532	113						

CD4 at second ART regimen (cells/μL)					<0.001			**<0.001**
≤50	344	212	Ref			Ref		
51-100	292	172	-40	(-77, -3)	0.035	**-37**	**(-74, 1)**	**0.054**
101-200	546	137	-72	(-104, -40)	<0.001	**-55**	**(-88, -22)**	**0.001**
201+	1274	75	-135	(-163, -106)	<0.001	**-115**	**(-147, -83)**	**<0.001**
Second ART regimen								**<0.001**
NRTI+NNRTI	1366	83	Ref			Ref		
NRTI+PI	973	165	85	(64, 105)	<0.001	**48**	**(26, 71)**	**<0.001**
Other	117	174	91	(46, 136)	<0.001	**71**	**(24, 117)**	**0.003**
Previous mono/duo exposure								
No	2272	119	Ref			Ref		
Yes	184	126	-5	(-41, 32)	0.803	-18	(-55, 19)	0.340
Hepatitis B co-infection								
Negative	843	99	Ref			Ref		
Positive	102	116	19	(-31, 68)	0.463	34	(-15, 82)	0.171
Not tested	1511	131						
Hepatitis C co-infection								
Negative	1118	109	Ref			Ref		
Positive	151	90	-35	(-80, 9)	0.117	-35	(-85, 14)	0.160
Not tested	1187	133						

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

11. Viral load response from start of second ART regimen

- VL <400 copies/mL from start of second ART regimen.
- Factors associated with VL <400 copies/mL at 12 months from start of second ART regimen.

11.1 Methods

Patients with at least one VL test after start of second ART regimen were included. Second ART was defined as a change of 2 drugs or 1 drug class change due to any reason. The proportion of VL <400 copies/ml was calculated as a fraction of patients with VL <400 copies/ml out of those who had VL testing for each time period, in Figure 35 and Figure 36. Factors associated with VL <400 copies/ml at 12 months after start of second ART was analysed using logistic regression model with site modelled as a random effect. Only patients with a VL test at 12 months after start of second ART were included in the regression analysis. The multivariate model is adjusted for all variables shown in Table 8.

11.2 Summary of results

The lower number of VL testing for patients in Cambodia, India, Indonesia and Vietnam who started second ART in the earlier years means the proportions of undetectable VL may be underestimated for these countries and care should be taken when interpreting the graphs. However, overall there seems to be an increase in the proportion of VL <400 copies/ml for those who switched between 2010-2013 compared to previous years. The multivariate model shows that starting a second ART between 2010-2013, with higher CD4 count at time of switch, and no prior mono/duo therapy were associated with having VL <400 copies/ml at 12 months from second ART. Favourable VL outcome (ie.<400 copies/mL) was also associated with those undertaking a combination therapy other than NRTI and NNRTI or PI based, though this occurred in only 101 cases.

Figure 35.VL <400 copies/mL from start of second ART regimen for each country by time period.

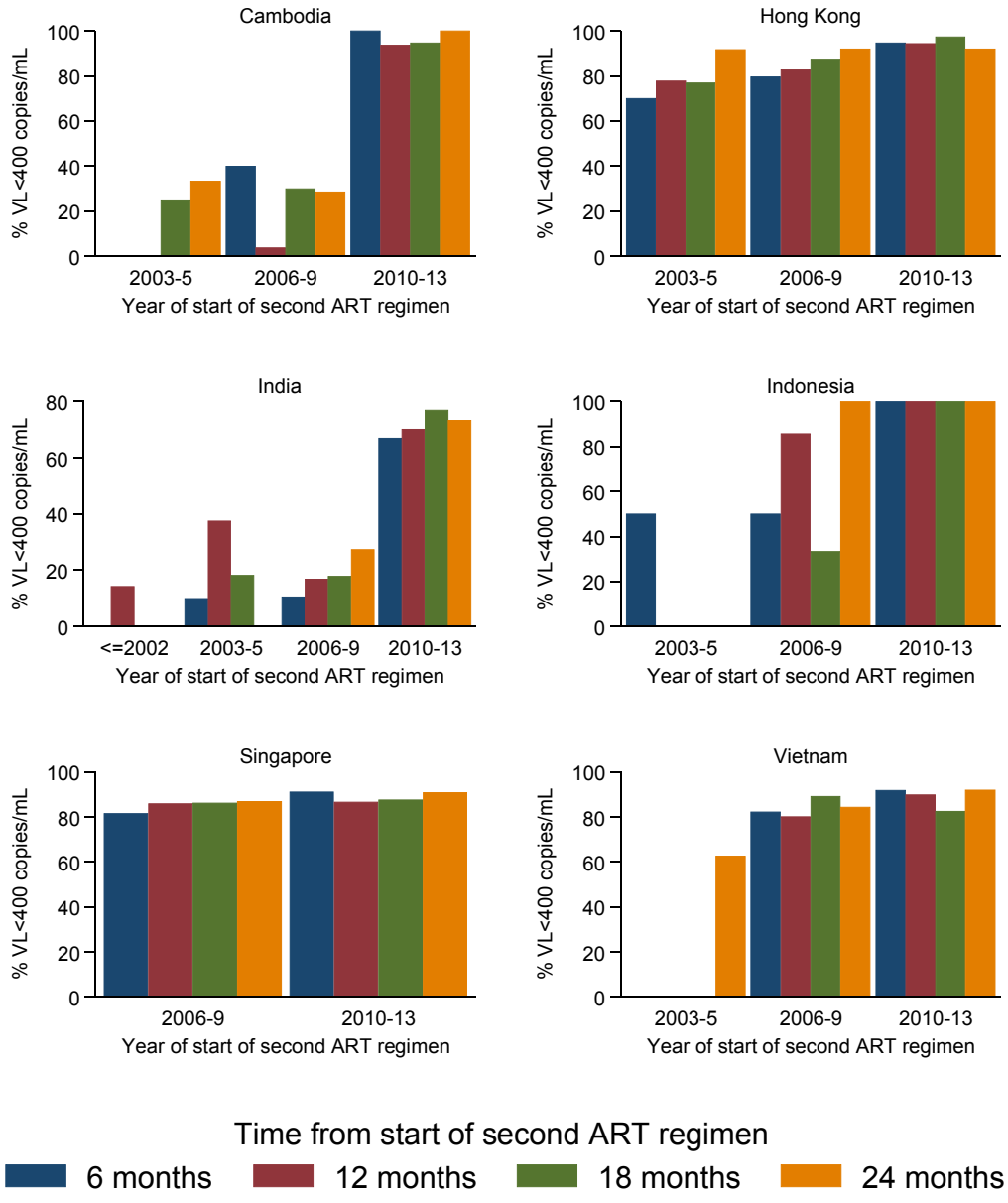


Figure 36.VL <400 copies/mL from start of second ART regimen for all countries by time period.

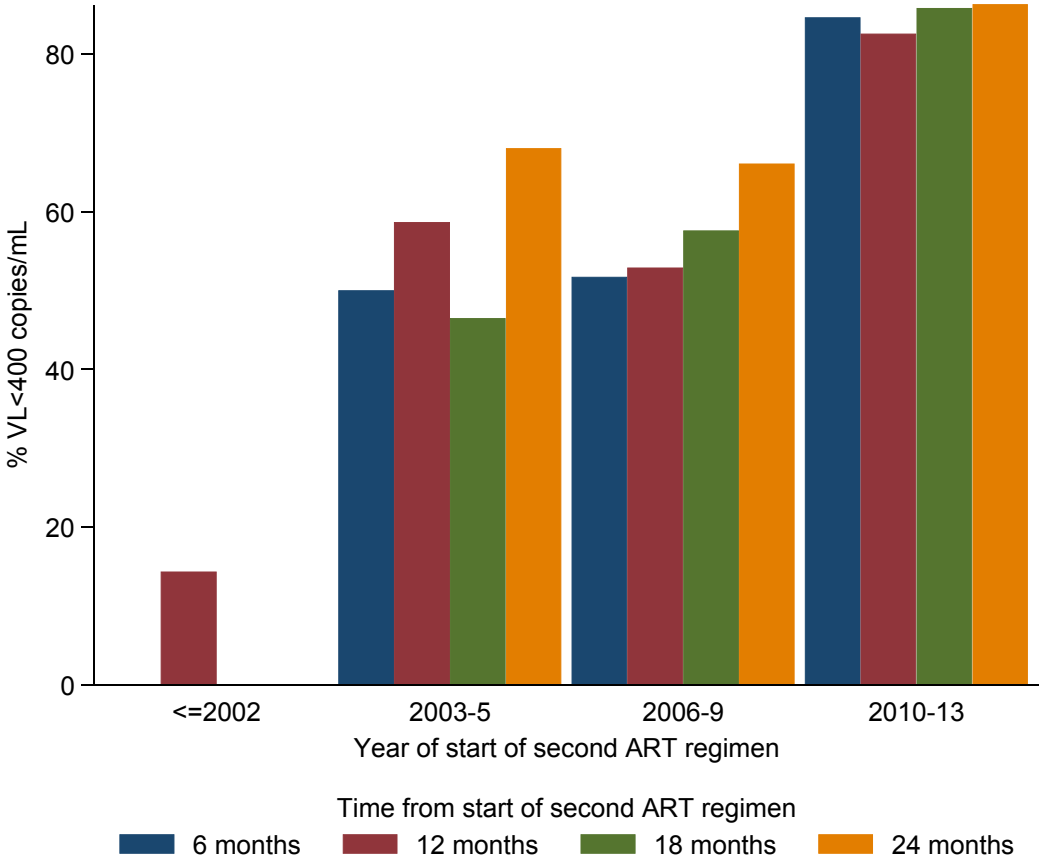


Table 8.VL <400 copies/mL at 12 months from start of second ART regimen.

	Number of patients	Number with VL <400 copies/mL	Univariate			Multivariate		
			OR	95% CI	p	OR	95% CI	p
Total	992	724						
Year of start of second ART regimen					<0.001			**<0.001**
≤2002	7	1	0.5	(0.1, 5.4)	0.598	0.5	(0.0, 5.4)	0.572
2003-2005	29	17	1			1		
2006-2009	280	148	1.2	(0.5, 3.1)	0.658	1.0	(0.4, 2.5)	0.941
2010-2013	676	558	6.5	(2.5, 16.6)	<0.001	**4.4**	**(1.7, 11.6)**	**0.003**
Age at start of second ART (years)					0.031			0.158
≤30	164	105	1			1		
31-40	412	295	1.7	(1.1, 2.6)	0.015	1.3	(0.8, 2.1)	0.247
41-50	241	182	1.9	(1.2, 3.1)	0.008	1.6	(0.9, 2.8)	0.099
51+	175	142	1.8	(1.0, 3.1)	0.039	1.5	(0.8, 2.9)	0.232
Sex								
Male	758	566	1			1		
Female	234	158	0.90	(0.7, 1.3)	0.701	1.0	(0.6, 1.5)	0.824
Mode of HIV Exposure					0.019			0.095
Heterosexual contact	707	481	1			1		
Homosexual contact	150	138	2.1	(1.1, 4.2)	0.029	1.8	(0.9, 3.8)	0.109
Injecting drug use	58	43	0.5	(0.2, 1.0)	0.044	0.5	(0.2, 1.3)	0.163
Other/unknown	77	62	1.2	(0.6, 2.3)	0.573	1.6	(0.8, 3.4)	0.213
Viral load at start of second ART regimen(copies/mL)								
≤100000	557	429	1			1		
>100000	150	108	0.9	(0.6, 1.4)	0.655	0.6	(0.4, 1.1)	0.107
Missing	285	187						

CD4 at start of second ART regimen (cells/µL)					<0.001			**0.004**
≤50	127	85	1			1		
51-100	99	66	1.5	(0.8, 2.8)	0.199	1.2	(0.6, 2.3)	0.644
101-200	178	140	3.1	(1.7, 5.7)	<0.001	**3.0**	**(1.5, 5.7)**	**0.001**
201+	515	379	2.5	(1.6, 4.1)	<0.001	**2.2**	**(1.2, 4.0)**	**0.010**
Missing	73	54						
Second ART regimen					<0.001			**0.005**
NRTI+NNRTI	410	272	1			1		
NRTI+PI	481	364	1.2	(0.9, 1.7)	0.204	1.2	(0.8, 1.7)	0.462
Other	101	88	5.7	(3.0, 11.0)	<0.001	**3.3**	**(1.6, 6.8)**	**0.001**
Previous mono/duo exposure								
No	936	690	1			1		
Yes	56	34	0.4	(0.2, 0.7)	0.001	**0.4**	**(0.2, 0.8)**	**0.006**
Hepatitis B co-infection								
Negative	483	393	1			1		
Positive	44	36	0.9	(0.4, 2.0)	0.744	1.0	(0.4, 2.5)	0.971
Not tested	465	295						
Hepatitis C co-infection								
Negative	611	501	1			1		
Positive	91	72	0.6	(0.3, 1.1)	0.109	0.8	(0.3, 1.8)	0.572
Not tested	290	151						

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

12. Mortality for ART patients

- Mortality from first regimen.
- Risk factors associated with mortality.

12.1 Methods

ART patients were excluded from the mortality analysis if their most recent clinic visit occurred on the same date as their ART initiation or if patients from Vietnam initiated ART prior to 2010. Patient follow up was censored at patient follow up time or most recent clinic visit (N=17 451). Mortality from first ART start for each country and for all countriesby time period was summarized using Kaplan-Meier curves in Figure 37 and Figure 38. Risk factors associated with mortality were assessed using Cox regression models stratified by site. The multivariate model is adjusted for all variables shown in Table 9.

12.2 Summary of results

For all countries, mortality rates were lowest in more recent time periods. Overall, mortality rates for those initiating ART prior to 2002 appear to be higher than those initiating ART between 2003-2005.However, this should not be overly interpreted as India is the only country contributing data for this time period and so, it is not representing an average across all the countries. Factors associated with increased risk of mortality include earlier years of ART initiation, older age at ART initiation, male gender, injecting drug use mode of HIV exposure, lower pre-ART CD4 cell count, first regimen containing NRTI+PI and previous mono/duo exposure.

Figure 37. Survival estimates for each country by time period.

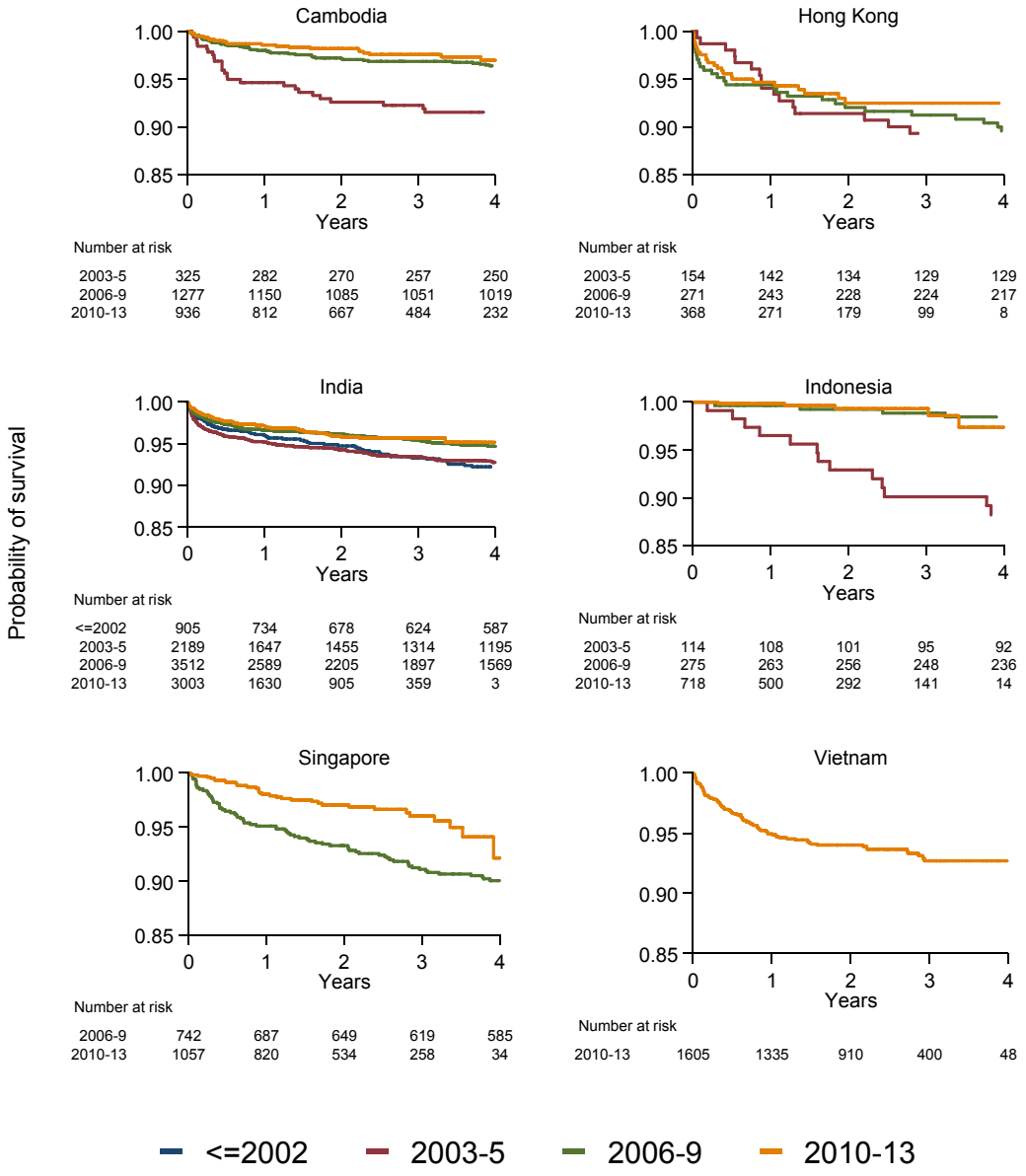
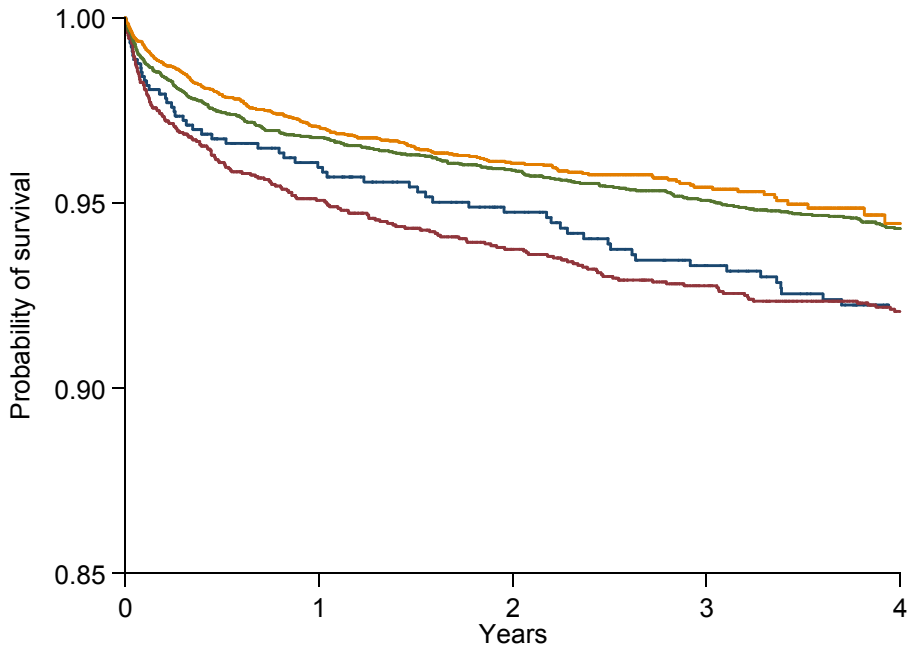


Figure 38. Survival estimates for all countries by time period.



Number at risk

<=2002	905	734	678	624	587
2003-5	2782	2179	1960	1795	1666
2006-9	6077	4932	4423	4039	3626
2010-13	7687	5368	3487	1741	339

Table 9. Risk factors associated with mortality.

	Number of patients	Deaths	Univariate			Multivariate		
			HR	95% CI	p	HR	95% CI	p
Total	17451	971						
Year of ART Initiation					<0.001			**0.005**
≤2002	905	91	0.89	(0.70, 1.15)	0.383	0.95	(0.73, 1.22)	0.680
2003-2005	2782	257	1			1		
2006-2009	6077	348	0.67	(0.56, 0.79)	<0.001	**0.77**	**(0.65, 0.92)**	**0.004**
2010-2013	7687	275	0.52	(0.42, 0.64)	<0.001	**0.72**	**(0.58, 0.90)**	**0.004**
Age at ART initiation (years)					<0.001			**<0.001**
≤30	4874	210	1			1		
31-40	7820	408	1.21	(1.02, 1.43)	0.025	1.09	(0.92, 1.30)	0.306
41-50	3234	191	1.40	(1.14, 1.70)	0.001	**1.25**	**(1.02, 1.54)**	**0.030**
51+	1523	162	2.47	(1.99, 3.06)	<0.001	**2.23**	**(1.78, 2.79)**	**<0.001**
Sex								
Male	12021	783	1			1		
Female	5430	188	0.58	(0.49, 0.69)	<0.001	**0.73**	**(0.62, 0.87)**	**<0.001**
Mode of HIV Exposure					<0.001			**<0.001**
Heterosexual contact	14357	773	1			1		
Homosexual contact	1087	44	0.52	(0.37, 0.73)	<0.001	0.78	(0.56, 1.10)	0.160
Injecting drug use	781	87	2.20	(1.67, 2.88)	<0.001	**1.95**	**(1.40, 2.74)**	**<0.001**
Other/unknown	1226	67	0.93	(0.72, 1.20)	0.599	1.00	(0.77, 1.29)	0.983
Pre-ART viral load (copies/mL)								
≤100000	1577	59	1			1		
>100000	1838	122	1.76	(1.29, 2.41)	<0.001	1.25	(0.91, 1.71)	0.169
Missing	14036	790						
Pre-ART CD4 (cells/µL)					<0.001			**<0.001**
≤50	3758	350	1			1		
51-100	2404	198	0.83	(0.69, 0.99)	0.038	0.85	(0.71, 1.01)	0.069
101-200	4018	194	0.46	(0.38, 0.55)	<0.001	**0.50**	**(0.41, 0.60)**	**<0.001**
201+	4693	95	0.22	(0.17, 0.27)	<0.001	**0.27**	**(0.21, 0.34)**	**<0.001**
Missing	2578	134						

First ART regimen					0.130			**0.032**
NRTI+NNRTI	16743	911	1			1		
NRTI+PI	639	56	1.33	(1.01, 1.76)	0.044	**1.46**	**(1.10, 1.94)**	**0.009**
Other/unknown	69	4	0.96	(0.36, 2.58)	0.938	1.25	(0.47, 3.37)	0.655
Previous mono/duo exposure								
No	16728	897	1			1		
Yes	723	74	1.52	(1.19, 1.93)	0.001	**1.39**	**(1.09, 1.78)**	**0.009**
Hepatitis B co-infection								
Negative	5811	331	1			1		
Positive	647	49	1.26	(0.94, 1.71)	0.126	1.15	(0.85, 1.56)	0.363
Not tested	10993	591						
Hepatitis C co-infection								
Negative	7199	383	1			1		
Positive	1029	88	1.69	(1.30, 2.20)	<0.001	1.08	(0.78, 1.49)	0.658
Not tested	9223	500						

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

13. Lost to Follow Up for ART patients

- Time to lost to follow up (LTFU) from first regimen.
- Risk factors associated with LTFU.

13.1 Methods

ART patients were considered LTFU if their most recent clinic visit was prior to 2013. ART patients were excluded from the LTFU analysis if their most recent clinic visit occurred on the same date as their ART initiation or if patients, from Vietnam, initiated ART prior to 2010. Patient follow up was censored at death or most recent clinic visit (N=17 451). The time to LTFU from first ART start for each country by time period was summarized using Kaplan-Meier curves in Figure 39.Risk factors associated with LTFU were assessed using Cox regression models stratified by site. The multivariate model is adjusted for all variables shown in Table 10.

13.2 Summary of results

LTFU rates show quite heterogeneous patterns across countries and time periods (Figure 39). India had the highest LTFU rates in comparison to all other countries with increasing LTFU rates in more recent time periods.However, many of these patients were transferred to other clinical sites in India, but this was not distinguishable from true LTFU in the current dataset. For other countries the rate of lost to follow-up was generally low across all time periods, mostly around 10% by four years. The combined figure of time to LTFU (Figure 40) is included for completeness and consistency with other sections of this report, but care should be taken not to over interpret this figure. The apparently clear improvement in LTFU in the most recent time period is almost certainly an artefact of combining such heterogeneous country data. In multivariate analyses, the most recent time periods had modestly increased rates of LTFU, probably mostly due to the influence of data from India. Other factors associated with increased risk of LTFU include younger age, male gender, injecting drug use mode of HIV exposure, lower pre-ART CD4 cell count, no previous mono/duo exposure and hepatitis C co-infection.

Figure 39. Time to lost to follow up from first ART start for each country by time period.

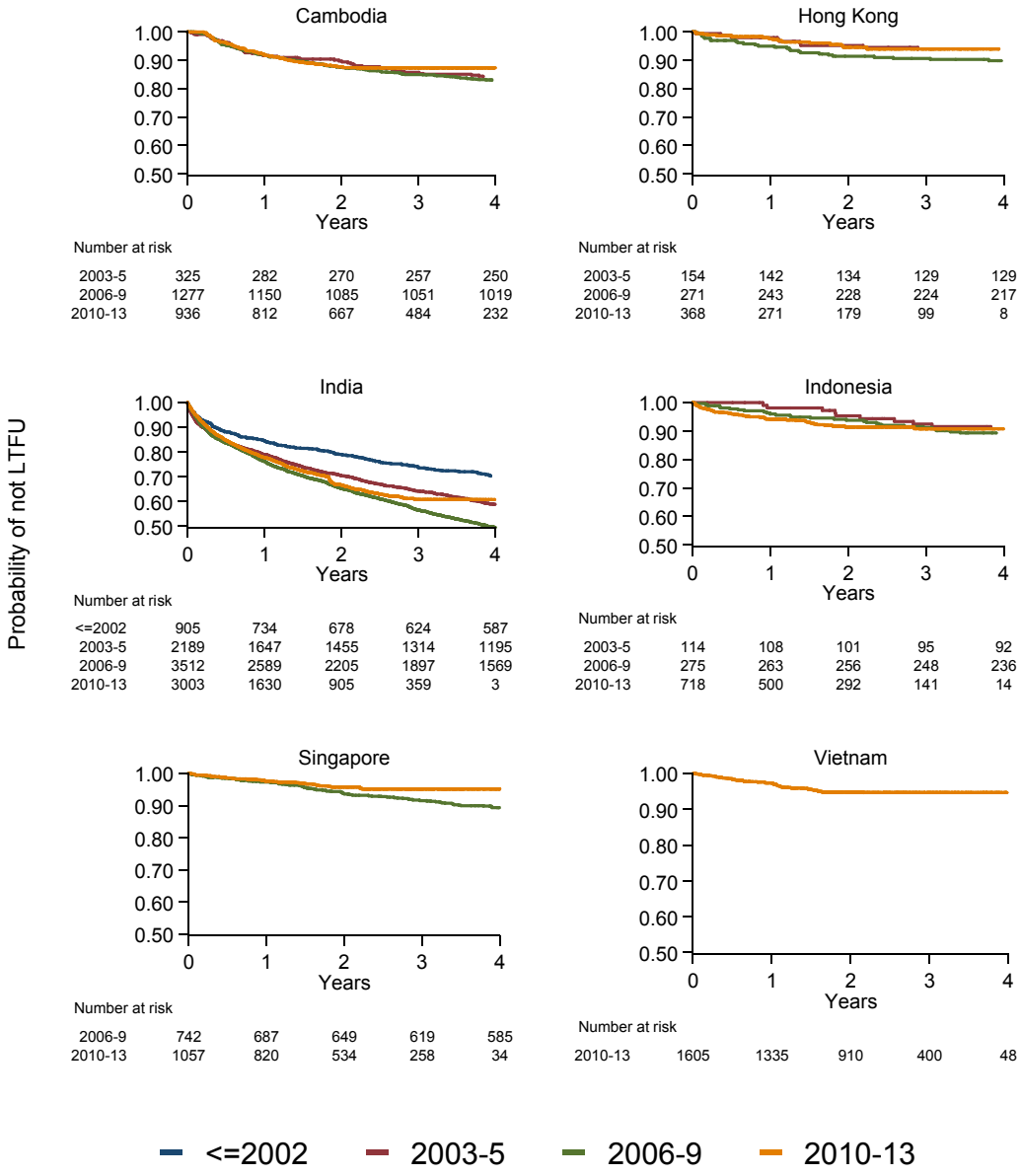
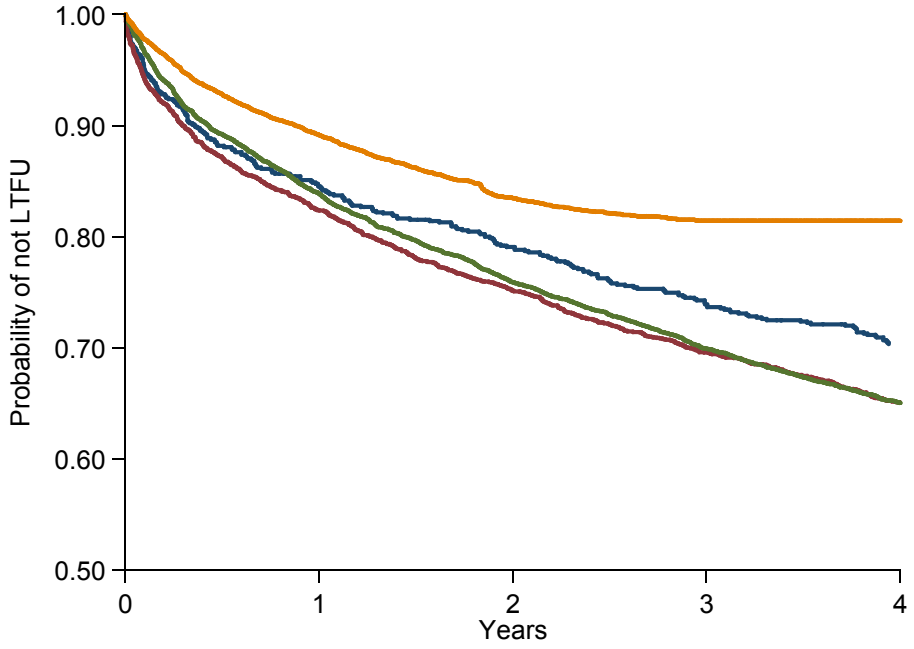


Figure 40. Time to lost to follow up from first ART start for all countries by time period.



Number at risk

<=2002	905	734	678	624	587
2003-5	2782	2179	1960	1795	1666
2006-9	6077	4932	4423	4039	3626
2010-13	7687	5368	3487	1741	339

Table 10. Risk factors associated to lost to follow up for each country.

	Number of patients	LTFU	Univariate			Multivariate		
			HR	95% CI	p	HR	95% CI	p
Total	17451	5526						
Year of ART Initiation					<0.001			**<0.001**
≤2002	905	500	0.63	(0.57, 0.70)	<0.001	**0.67**	**(0.60, 0.74)**	**<0.001**
2003-2005	2782	1494	1			1.00		
2006-2009	6077	2406	1.19	(1.11, 1.27)	<0.001	**1.27**	**(1.18, 1.36)**	**<0.001**
2010-2013	7687	1126	1.02	(0.94, 1.12)	0.586	**1.22**	**(1.12, 1.33)**	**<0.001**
Age at ART initiation (years)					0.216			**0.001**
≤30	4874	1611	1			1.00		
31-40	7820	2665	0.98	(0.92, 1.04)	0.568	**0.91**	**(0.85, 0.97)**	**0.004**
41-50	3234	914	0.95	(0.88, 1.03)	0.234	**0.87**	**(0.80, 0.95)**	**0.001**
51+	1523	336	0.95	(0.85, 1.07)	0.433	**0.88**	**(0.78, 0.99)**	**0.032**
Sex								
Male	12021	3937	1			1.00		
Female	5430	1589	0.92	(0.87, 0.98)	0.008	**0.91**	**(0.86, 0.97)**	**0.003**
Mode of HIV Exposure					<0.001			**<0.001**
Heterosexual contact	14357	5039	1			1.00		
Homosexual contact	1087	87	0.98	(0.77, 1.25)	0.879	1.02	(0.80, 1.29)	0.890
Injecting drug use	781	125	1.73	(1.42, 2.11)	<0.001	**1.60**	**(1.28, 2.01)**	**<0.001**
Other/unknown	1226	275	0.82	(0.73, 0.93)	0.001	**0.85**	**(0.75, 0.96)**	**0.007**
Pre-ART viral load (copies/mL)								
≤100000	1577	218	1			1.00		
>100000	1838	296	1.14	(0.96, 1.36)	0.136	1.04	(0.87, 1.24)	0.698
Missing	14036	5012						
Pre-ART CD4 (cells/µL)					<0.001			**<0.001**
≤50	3758	977	1			1.00		
51-100	2404	891	0.91	(0.83, 1.00)	0.054	**0.90**	**(0.82, 0.99)**	**0.029**
101-200	4018	1523	0.80	(0.73, 0.86)	<0.001	**0.78**	**(0.71, 0.84)**	**<0.001**
201+	4693	1032	0.63	(0.58, 0.69)	<0.001	**0.67**	**(0.61, 0.73)**	**<0.001**
Missing	2578	1103						

First ART regimen					0.048			0.689
NRTI+NNRTI	16743	5353	1			1.00		
NRTI+PI	639	163	0.84	(0.72, 0.98)	0.027	0.97	(0.82, 1.13)	0.674
Other/unknown	69	10	0.70	(0.38, 1.31)	0.267	0.79	(0.42, 1.46)	0.446
Previous mono/duo exposure								
No	16728	5249	1			1.00		
Yes	723	277	0.80	(0.71, 0.91)	<0.001	**0.87**	**(0.77, 0.99)**	**0.031**
Hepatitis B co-infection								
Negative	5811	644	1			1.00		
Positive	647	83	1.20	(0.95, 1.50)	0.126	1.13	(0.90, 1.43)	0.283
Not tested	10993	4799						
Hepatitis C co-infection								
Negative	7199	1036	1			1.00		
Positive	1029	139	1.65	(1.37, 2.00)	<0.001	**1.40**	**(1.14, 1.73)**	**0.002**
Not tested	9223	4351						

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

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