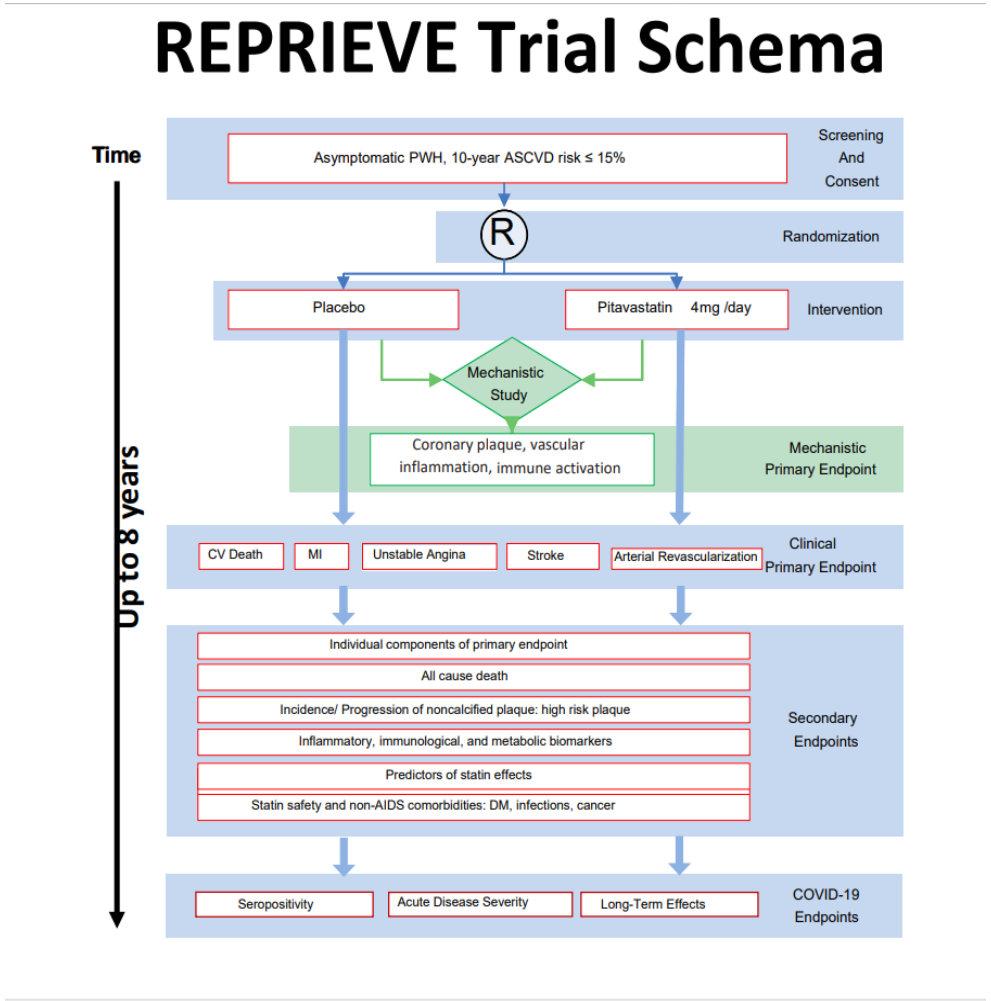
Should we treat all people living with HIV above 40 years with a statin?

Yvonne Gilleece
Brighton & Sussex Medical School
University Hospitals Sussex NHS Trust
Chair of the British HIV Association

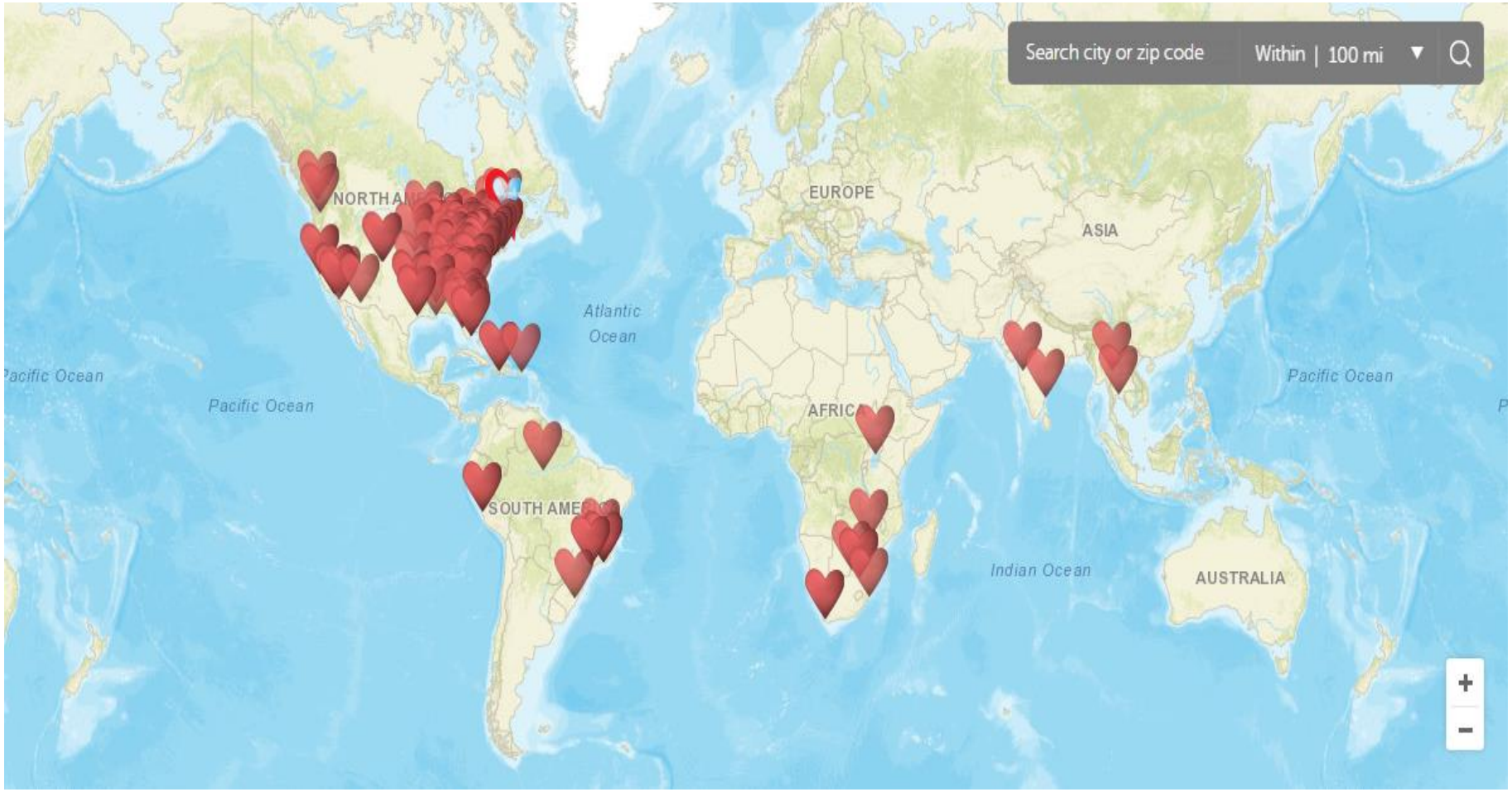
YES!!!

REPRIEVE Study Summary

- **Goal:** To evaluate pitavastatin compared with placebo among individuals with human immunodeficiency virus (HIV) infection and low-to-moderate risk of cardiovascular disease
- **Study Design:** Randomized, prospective, parallel, placebo controlled, stratified
- **Total number of enrollees:** 7,769
- **Duration of follow-up:** median 5.1 years
- **Mean patient age:** 50 years
- **Percentage female:** 31%
- **Inclusion criteria:**
  - Individuals with HIV infection 40-75 years of age
  - Stable anti-retroviral therapy
- **Exclusion criteria:**
  - Statin use within the last 90 days
  - Known atherosclerotic cardiovascular disease
- Median screening low-density lipoprotein cholesterol (LDL-C): 108 mg/dL
- **Median CD4 count:** 621 cells/mm^3
- **HIV RNA value below quantification:** 5,250 of 5,997 participants (87.5%)



REPRIEVE Study Sites



REPRIEVE Principal Findings

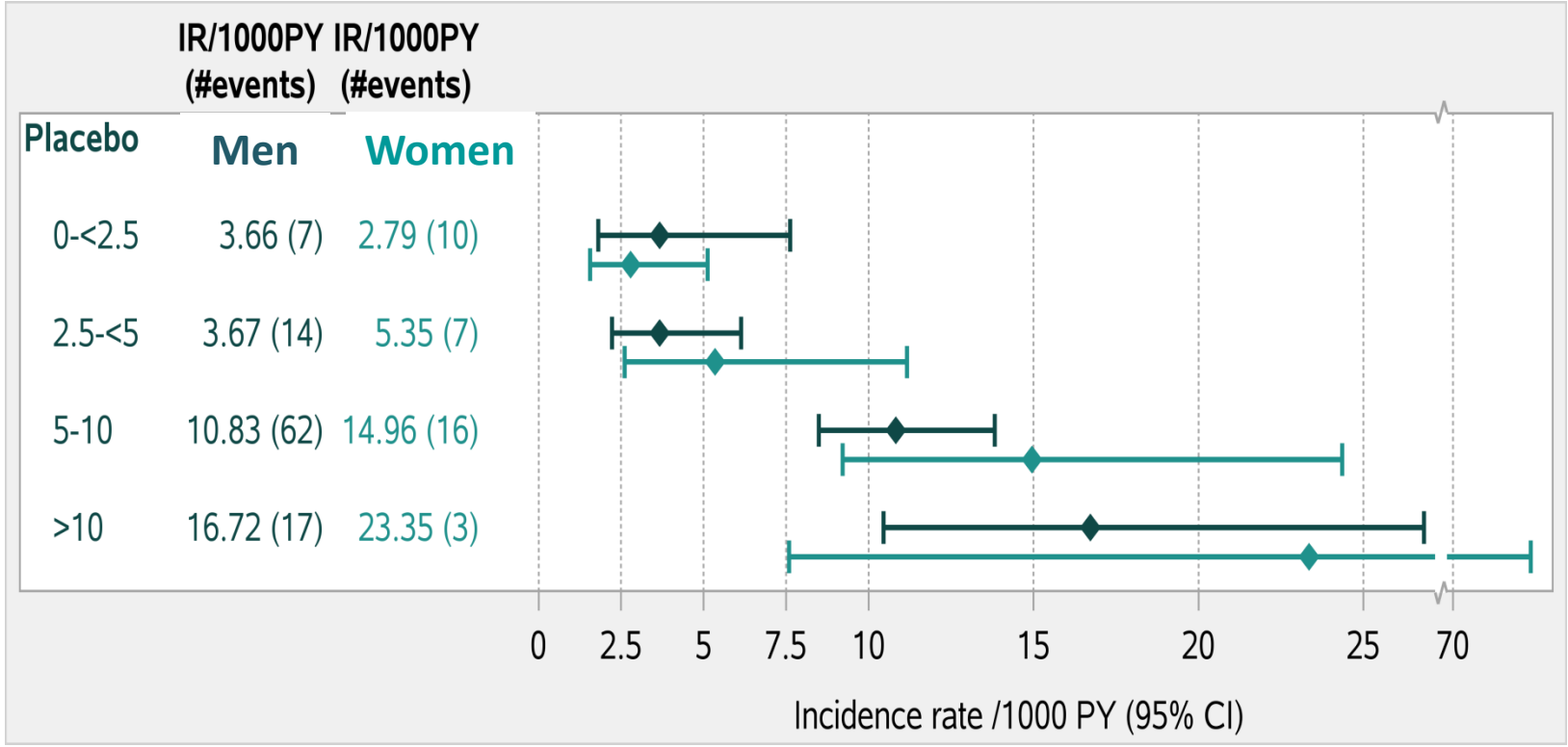
Primary outcome (incidence of major adverse cardiovascular events, MACE): occurred in **4.81** per 1,000 person-years in the pitavastatin group vs. **7.32** per 1,000 person-years in the placebo group (p = 0.002)

Secondary outcomes:

- Cardiovascular death: 0.64 per 1,000 person-years in the pitavastatin group vs. 0.85 per 1,000 person-years in the placebo group (p = not significant [NS])
- Nonfatal serious adverse event: 4.16 per 1,000 person-years in the pitavastatin group vs. 4.13 per 1,000 person-years in the placebo group (p = NS)
- Myalgia, muscle weakness, or myopathy grade ≥3, or treatment-limiting: **0.49** per 1,000 person-years in the pitavastatin group vs. **0.28** per 1,000 person-years in the placebo group (p < 0.05)

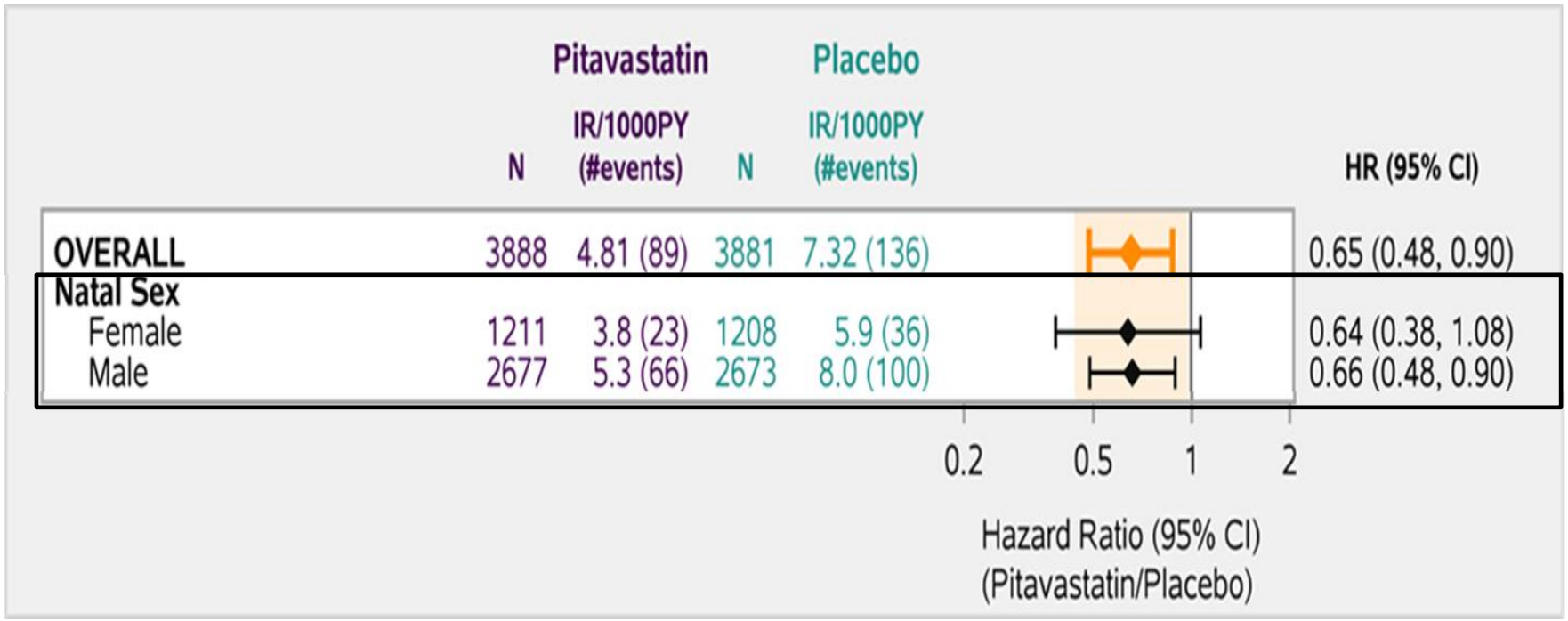
- <u>Mechanistic substudy (n = 804):</u>
- Change in noncalcified plaque volume at 2 years: -1.7 mm^3 with pitavastatin vs. 2.6 mm^3 with placebo (p = 0.044)
- Change in LDL-C: -29 mg/dL with pitavastatin vs. 0 with placebo
- Change in Lp-PLA2: -10.1 ng/dL with pitavastatin vs. 19.3 with placebo (p < 0.001)
- Change in oxLDL: -14.9 U/L with pitavastatin vs. -6.45 with placebo (p < 0.001)
- Change in hs-CRP: -0.1 mg/L with pitavastatin vs. 0.1 with placebo (p = 0.09)

MACE Rates in 10-year ASCVD Risk Score Subgroups by Sex

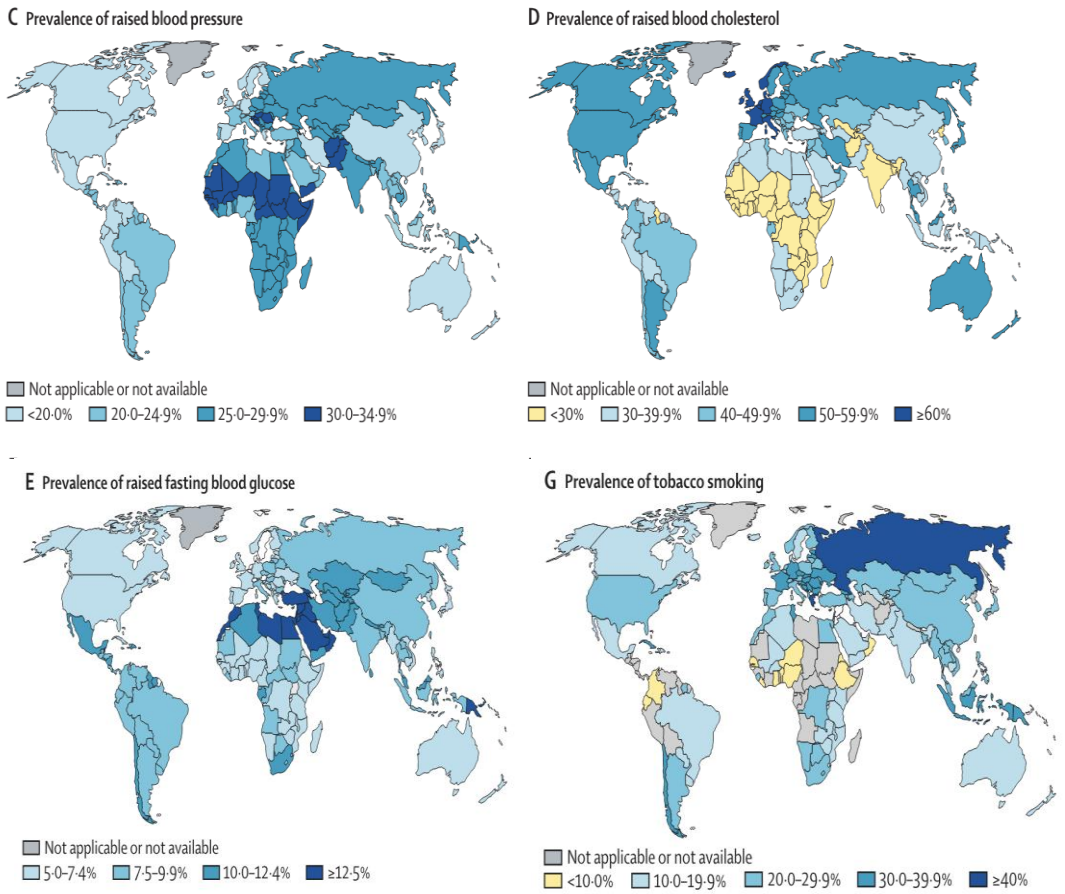


- Might 10y ASCVD risk score underestimate risk in women > men?
- Is it possible that systemic immune activation (not well captured by ASCVD risk score) is driving MACE to a greater extent in women (vs.men) living with HIV?

Effect Size of Statin Rx to Reduce MACE Consistent among Women vs. Men



Distribution of cardiovascular disease risk factors in PWH varies by geographical location



Lancet HIV 2020; 7: e279–93

REPRIEVE Interpretation

- Among individuals with living with HIV and low-to-moderate risk of cardiovascular disease, pitavastatin treatment was beneficial
- Pitavastatin vs. placebo was associated with a reduction in major adverse cardiovascular events
  - may be mediated by decreased risk of plaque progression, decreased lipid oxidation, and decreased arterial inflammation
- The results were the same in various tested subgroups (gender, **geographic region**, CD4 level, etc.)
- The benefit observed with pitavastatin was more than predicted by the degree of LDL-C lowering
- Pitavastatin treatment was safe with similar incidence of nonfatal serious adverse events; however, muscle-related symptoms were more common vs. placebo, but did not reach significance
- Might 10y ASCVD risk score underestimate risk in women > men?
- Is it possible that systemic immune activation (not well captured by ASCVD risk score) is driving MACE to a greater extent in women (vs.men) living with HIV?

Years of Life Lost 2000-2021 by World Bank Region – Global

Global

2021				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	2,105,584	100.0	26520.7
1	COVID-19	228,582	10.9	2879.1
2	Ischaemic heart disease	189,840	9.0	2391.1
3	Stroke	145,126	6.9	1827.9
4	Lower respiratory infections	105,197	5.0	1325.0
5	Preterm birth complications	86,517	4.1	1089.7
6	Chronic obstructive pulmonary disease	63,344	3.0	797.8
7	Diarrhoeal diseases	62,148	3.0	782.8
8	Road injury	59,555	2.8	750.1
9	Tuberculosis	56,216	2.7	708.1
10	Birth asphyxia and birth trauma	54,932	2.6	691.9
11	Malaria	49,726	2.4	626.3
12	Congenital anomalies	45,480	2.2	572.8
13	Cirrhosis of the liver	45,329	2.2	570.9
14	Trachea, bronchus, lung cancers	45,070	2.1	567.7
15	Diabetes mellitus	39,463	1.9	497.1
16	HIV/AIDS	35,946	1.7	452.8
17	Kidney diseases	34,973	1.7	440.5
18	Self-harm	33,214	1.6	418.3
19	Interpersonal violence	27,932	1.3	351.8
20	Hypertensive heart disease	26,207	1.2	330.1

2000				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	2,202,242	100.0	35759.6
1	Lower respiratory infections	179,190	8.1	2909.7
2	Diarrhoeal diseases	145,458	6.6	2361.9
3	Ischaemic heart disease	141,186	6.4	2292.6
4	Preterm birth complications	139,637	6.3	2267.4
5	Stroke	127,423	5.8	2069.1
6	Tuberculosis	112,380	5.1	1824.8
7	Birth asphyxia and birth trauma	97,710	4.4	1586.6
8	HIV/AIDS	97,519	4.4	1583.5
9	Malaria	74,985	3.4	1217.6
10	Road injury	66,387	3.0	1078.0
11	Measles	65,776	3.0	1068.0
12	Chronic obstructive pulmonary disease	56,368	2.6	915.3
13	Congenital anomalies	50,000	2.3	811.9
14	Other neonatal conditions	39,717	1.8	644.9
15	Cirrhosis of the liver	39,232	1.8	637.0
16	Self-harm	37,834	1.7	614.3
17	Trachea, bronchus, lung cancers	33,076	1.5	537.1
18	Meningitis	28,772	1.3	467.2
19	Protein-energy malnutrition	28,636	1.3	465.0
20	Neonatal sepsis and infections	28,366	1.3	460.6

Years of Life Lost 2000-2021 by World Bank Region – Global

Global

2021				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Caus			
1	COVID-1			
2	Ischaem			
3	Stroke			
4	Lower re			
5	Preterm			
6	Chronic			
7	Diarrhoe			
8	Road inj			
9	Tubercul			
10	Birth asp			
11	Malaria			
12	Congenital anomalies	45,480	2.2	572.6
13	Cirrhosis of the liver	45,329	2.2	570.9
14	Trachea, bronchus, lung cancers	45,070	2.1	567.7
15	Diabetes mellitus	39,463	1.9	497.1
16	HIV/AIDS	35,946	1.7	452.8
17	Kidney diseases	34,973	1.7	440.5
18	Self-harm	33,214	1.6	418.3
19	Interpersonal violence	27,932	1.3	351.8
20	Hypertensive heart disease	26,207	1.2	330.1

2000				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
			100.0	35759.6
			8.1	2909.7
			6.6	2361.9
			6.4	2292.6
			6.3	2267.4
			5.8	2069.1
			5.1	1824.8
			4.4	1586.6
			4.4	1583.5
			3.4	1217.6
			3.0	1078.0
			3.0	1068.0
12	Chronic obstructive pulmonary disease	50,568	2.6	915.3
13	Congenital anomalies	50,000	2.3	811.9
14	Other neonatal conditions	39,717	1.8	644.9
15	Cirrhosis of the liver	39,232	1.8	637.0
16	Self-harm	37,834	1.7	614.3
17	Trachea, bronchus, lung cancers	33,076	1.5	537.1
18	Meningitis	28,772	1.3	467.2
19	Protein-energy malnutrition	28,636	1.3	465.0
20	Neonatal sepsis and infections	28,366	1.3	460.6

The world's biggest killer is ischaemic heart disease, responsible for 13% of the world's total deaths

Since 2000, the largest increase in deaths has been for this disease, rising by 2.7 million to 9.0 million deaths in 2021

Years of Life Lost 2000-2021 by World Bank Region - HIC

High-income economies

2021				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	292,460	100.0	21413.2
1	Ischaemic heart disease	37,975	13.0	2780.4
2	COVID-19	37,587	12.9	2752.0
3	Stroke	17,753	6.1	1299.8
4	Trachea, bronchus, lung cancers	13,435	4.6	983.7
5	Alzheimer disease and other dementias	8,946	3.1	655.0
6	Chronic obstructive pulmonary disease	8,233	2.8	602.8
7	Self-harm	8,193	2.8	599.8
8	Colon and rectum cancers	7,673	2.6	561.8
9	Cirrhosis of the liver	7,281	2.5	533.1
10	Drug use disorders	6,800	2.3	497.9
11	Lower respiratory infections	5,691	1.9	416.7
12	Kidney diseases	5,297	1.8	387.8
13	Breast cancer	5,206	1.8	381.1
14	Diabetes mellitus	5,085	1.7	372.3
15	Road injury	5,073	1.7	371.5
16	Pancreas cancer	4,943	1.7	361.9
17	Hypertensive heart disease	4,845	1.7	354.8
18	Cardiomyopathy, myocarditis, endocarditis	4,067	1.4	297.8
19	Stomach cancer	3,431	1.2	251.2
20	Liver cancer	3,181	1.1	232.9

2000				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	267,606	100.0	21959.5
1	Ischaemic heart disease	50,743	19.0	4163.9
2	Stroke	26,927	10.1	2209.6
3	Trachea, bronchus, lung cancers	14,156	5.3	1161.6
4	Self-harm	10,349	3.9	849.2
5	Road injury	10,008	3.7	821.2
6	Chronic obstructive pulmonary disease	8,051	3.0	660.7
7	Lower respiratory infections	7,561	2.8	620.5
8	Colon and rectum cancers	7,169	2.7	588.3
9	Cirrhosis of the liver	6,114	2.3	501.7
10	Breast cancer	5,380	2.0	441.4
11	Stomach cancer	5,127	1.9	420.7
12	Cardiomyopathy, myocarditis, endocarditis	4,154	1.6	340.8
13	Congenital anomalies	4,149	1.6	340.4
14	Diabetes mellitus	4,083	1.5	335.0
15	Interpersonal violence	3,931	1.5	322.6
16	Alcohol use disorders	3,476	1.3	285.2
17	Kidney diseases	3,427	1.3	281.2
18	Lymphomas, multiple myeloma	3,267	1.2	268.1
19	Pancreas cancer	3,179	1.2	260.9
20	Preterm birth complications	3,110	1.2	255.2

Years of Life Lost 2000-2021 by World Bank Region - UMIC

Upper-middle-income economies

2021				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	603,160	100.0	21399.0
1	Stroke	72,114	12.0	2558.5
2	COVID-19	71,784	11.9	2546.8
3	Ischaemic heart disease	69,237	11.5	2456.4
4	Trachea, bronchus, lung cancers	24,969	4.1	885.8
5	Chronic obstructive pulmonary disease	24,850	4.1	881.6
6	Road injury	21,777	3.6	772.6
7	Lower respiratory infections	14,540	2.4	515.8
8	Diabetes mellitus	13,553	2.2	480.8
9	Stomach cancer	13,386	2.2	474.9
10	Cirrhosis of the liver	12,888	2.1	457.2
11	Kidney diseases	12,332	2.0	437.5
12	Interpersonal violence	11,835	2.0	419.9
13	Congenital anomalies	10,563	1.8	374.7
14	Colon and rectum cancers	10,441	1.7	370.4
15	Tuberculosis	10,092	1.7	358.0
16	Hypertensive heart disease	9,794	1.6	347.5
17	Self-harm	9,133	1.5	324.0
18	HIV/AIDS	9,077	1.5	322.0
19	Preterm birth complications	9,058	1.5	321.4
20	Alzheimer disease and other dementias	8,918	1.5	316.4

2000				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	566,777	100.0	23842.6
1	Stroke	64,032	11.3	2693.6
2	Ischaemic heart disease	46,344	8.2	1949.5
3	Chronic obstructive pulmonary disease	30,746	5.4	1293.4
4	Lower respiratory infections	29,312	5.2	1233.1
5	Road injury	27,051	4.8	1137.9
6	Preterm birth complications	25,991	4.6	1093.4
7	Congenital anomalies	20,182	3.6	849.0
8	HIV/AIDS	17,822	3.1	749.7
9	Birth asphyxia and birth trauma	17,550	3.1	738.3
10	Tuberculosis	17,374	3.1	730.9
11	Trachea, bronchus, lung cancers	15,388	2.7	647.3
12	Stomach cancer	13,998	2.5	588.8
13	Diarrhoeal diseases	13,843	2.4	582.3
14	Cirrhosis of the liver	13,401	2.4	563.7
15	Interpersonal violence	12,953	2.3	544.9
16	Self-harm	12,492	2.2	525.5
17	Drowning	9,668	1.7	406.7
18	Kidney diseases	8,355	1.5	351.5
19	Diabetes mellitus	7,935	1.4	333.8
20	Oesophagus cancer	7,456	1.3	313.6

Years of Life Lost 2000-2021 by World Bank Region - LMIC

Lower-middle-income economies

2021				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	914,416	100.0	30430.4
1	COVID-19	110,318	12.1	3671.2
2	Ischaemic heart disease	73,077	8.0	2431.9
3	Lower respiratory infections	56,643	6.2	1885.0
4	Preterm birth complications	50,916	5.6	1694.4
5	Stroke	44,906	4.9	1494.4
6	Diarrhoeal diseases	40,853	4.5	1359.5
7	Tuberculosis	35,403	3.9	1178.2
8	Birth asphyxia and birth trauma	34,836	3.8	1159.3
9	Chronic obstructive pulmonary disease	27,757	3.0	923.7
10	Malaria	26,571	2.9	884.3
11	Congenital anomalies	24,724	2.7	822.8
12	Road injury	23,754	2.6	790.5
13	Cirrhosis of the liver	20,424	2.2	679.7
14	Diabetes mellitus	17,342	1.9	577.1
15	HIV/AIDS	15,748	1.7	524.1
16	Self-harm	13,476	1.5	448.4
17	Kidney diseases	13,463	1.5	448.0
18	Other neonatal conditions	12,744	1.4	424.1
19	Drowning	10,163	1.1	338.2
20	Neonatal sepsis and infections	9,965	1.1	331.6

2000				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	1,023,555	100.0	48150.7
1	Lower respiratory infections	102,378	10.0	4816.1
2	Diarrhoeal diseases	100,008	9.8	4704.6
3	Preterm birth complications	85,470	8.4	4020.7
4	Tuberculosis	74,419	7.3	3500.9
5	Birth asphyxia and birth trauma	63,114	6.2	2969.0
6	HIV/AIDS	51,447	5.0	2420.2
7	Measles	41,524	4.1	1953.4
8	Malaria	40,287	3.9	1895.2
9	Ischaemic heart disease	38,462	3.8	1809.4
10	Stroke	29,362	2.9	1381.3
11	Other neonatal conditions	26,821	2.6	1261.7
12	Road injury	21,959	2.1	1033.0
13	Congenital anomalies	20,846	2.0	980.7
14	Neonatal sepsis and infections	19,545	1.9	919.5
15	Maternal conditions	16,598	1.6	780.8
16	Cirrhosis of the liver	16,507	1.6	776.6
17	Chronic obstructive pulmonary disease	16,044	1.6	754.7
18	Meningitis	15,977	1.6	751.6
19	Protein-energy malnutrition	15,442	1.5	726.4
20	Whooping cough	14,837	1.4	698.0

Years of Life Lost 2000-2021 by World Bank Region-LIC

Low-income economies

2021				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	284,592	100.0	40760.0
1	Lower respiratory infections	27,933	9.8	4000.6
2	Preterm birth complications	24,733	8.7	3542.3
3	Malaria	22,958	8.1	3288.1
4	Diarrhoeal diseases	16,980	6.0	2431.9
5	Birth asphyxia and birth trauma	15,335	5.4	2196.4
6	Tuberculosis	10,020	3.5	1435.1
7	Stroke	9,739	3.4	1394.9
8	HIV/AIDS	8,948	3.1	1281.5
9	Road injury	8,678	3.0	1242.8
10	COVID-19	8,435	3.0	1208.0
11	Ischaemic heart disease	8,396	3.0	1202.4
12	Congenital anomalies	7,377	2.6	1056.5
13	Collective violence and legal intervention	7,131	2.5	1021.4
14	Other neonatal conditions	6,004	2.1	859.9
15	Measles	5,706	2.0	817.3
16	Maternal conditions	5,495	1.9	787.0
17	Meningitis	5,193	1.8	743.8
18	Protein-energy malnutrition	4,523	1.6	647.7
19	Cirrhosis of the liver	4,419	1.6	632.9
20	Neonatal sepsis and infections	4,098	1.4	586.9

2000				
Rank	Cause	YLLs (000s)	% YLL	YLLs per 100,000
0	All Causes	336,413	100.0	86242.1
1	Lower respiratory infections	39,656	11.8	10166.0
2	Malaria	34,400	10.2	8818.6
3	Diarrhoeal diseases	31,111	9.2	7975.5
4	HIV/AIDS	26,281	7.8	6737.4
5	Preterm birth complications	24,743	7.4	6343.1
6	Measles	21,522	6.4	5517.3
7	Tuberculosis	18,475	5.5	4736.2
8	Birth asphyxia and birth trauma	16,060	4.8	4117.1
9	Protein-energy malnutrition	9,682	2.9	2482.1
10	Meningitis	9,042	2.7	2317.9
11	Maternal conditions	6,892	2.0	1766.9
12	Road injury	6,848	2.0	1755.6
13	Stroke	6,588	2.0	1688.9
14	Other neonatal conditions	6,279	1.9	1609.6
15	Collective violence and legal intervention	5,844	1.7	1498.3
16	Ischaemic heart disease	5,059	1.5	1296.9
17	Neonatal sepsis and infections	4,823	1.4	1236.5
18	Whooping cough	4,639	1.4	1189.2
19	Congenital anomalies	4,565	1.4	1170.3
20	Cirrhosis of the liver	2,898	0.9	742.8

Global Health Estimates Disability Adjusted Life Years 2000-2021

Global

2021				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	**All Causes**	**3,013,403**	**100.0**	**37955.1**
1	COVID-19	242,926	8.1	3059.8
2	Ischaemic heart disease	193,833	6.4	2441.4
3	Stroke	160,227	5.3	2018.1
4	Lower respiratory infections	105,645	3.5	1330.6
5	Preterm birth complications	100,485	3.3	1265.7
6	Back and neck pain	90,900	3.0	1144.9
7	Diabetes mellitus	80,550	2.7	1014.6
8	Chronic obstructive pulmonary disease	78,067	2.6	983.3
9	Diarrhoeal diseases	69,748	2.3	878.5
10	Road injury	67,826	2.3	854.3
11	Tuberculosis	60,642	2.0	763.8
12	Birth asphyxia and birth trauma	59,261	2.0	746.4
13	Depressive disorders	56,674	1.9	713.8
14	Congenital anomalies	52,725	1.7	664.1
15	Malaria	52,060	1.7	655.7
16	Cirrhosis of the liver	45,937	1.5	578.6
17	Trachea, bronchus, lung cancers	45,609	1.5	574.5
18	Other hearing loss	44,186	1.5	556.5
19	Falls	43,843	1.5	552.2
20	Kidney diseases	43,720	1.5	550.7

2000				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	**All Causes**	**2,841,210**	**100.0**	**46135.0**
1	Lower respiratory infections	179,624	6.3	2916.7
2	Diarrhoeal diseases	152,478	5.4	2475.9
3	Preterm birth complications	149,165	5.3	2422.1
4	Ischaemic heart disease	143,502	5.1	2330.2
5	Stroke	137,152	4.8	2227.0
6	Tuberculosis	117,430	4.1	1906.9
7	HIV/AIDS	100,571	3.5	1633.1
8	Birth asphyxia and birth trauma	99,860	3.5	1621.5
9	Malaria	77,510	2.7	1258.6
10	Road injury	74,676	2.6	1212.6
11	Measles	65,914	2.3	1070.3
12	Chronic obstructive pulmonary disease	65,277	2.3	1059.9
13	Back and neck pain	63,141	2.2	1025.3
14	Congenital anomalies	56,220	2.0	912.9
15	Other neonatal conditions	40,534	1.4	658.2
16	Cirrhosis of the liver	39,730	1.4	645.1
17	Self-harm	38,789	1.4	629.8
18	Diabetes mellitus	38,102	1.3	618.7
19	Depressive disorders	36,952	1.3	600.0
20	Trachea, bronchus, lung cancers	33,408	1.2	542.5

Global Health Estimates Disability Adjusted Life Years 2000-2021 - HIC

High-income economies

2021				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	All Causes	489,396	100.0	35832.5
1	COVID-19	39,608	8.1	2900.0
2	Ischaemic heart disease	39,097	8.0	2862.6
3	Back and neck pain	25,190	5.1	1844.3
4	Stroke	21,486	4.4	1573.2
5	Diabetes mellitus	15,975	3.3	1169.7
6	Trachea, bronchus, lung cancers	13,649	2.8	999.3
7	Alzheimer disease and other dementias	13,314	2.7	974.8
8	Depressive disorders	11,773	2.4	862.0
9	Drug use disorders	11,643	2.4	852.5
10	Chronic obstructive pulmonary disease	11,456	2.3	838.8
11	Falls	11,415	2.3	835.8
12	Anxiety disorders	9,647	2.0	706.3
13	Other hearing loss	8,766	1.8	641.8
14	Migraine	8,491	1.7	621.7
15	Self-harm	8,372	1.7	613.0
16	Skin diseases	8,217	1.7	601.6
17	Colon and rectum cancers	8,208	1.7	600.9
18	Cirrhosis of the liver	7,399	1.5	541.7
19	Kidney diseases	7,380	1.5	540.4
20	Road injury	7,141	1.5	522.8

2000				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	All Causes	423,180	100.0	34725.8
1	Ischaemic heart disease	51,633	12.2	4237.0
2	Stroke	29,977	7.1	2459.9
3	Back and neck pain	21,022	5.0	1725.0
4	Trachea, bronchus, lung cancers	14,330	3.4	1175.9
5	Road injury	12,821	3.0	1052.1
6	Self-harm	10,536	2.5	864.6
7	Chronic obstructive pulmonary disease	10,314	2.4	846.3
8	Falls	9,726	2.3	798.1
9	Diabetes mellitus	9,039	2.1	741.7
10	Depressive disorders	8,948	2.1	734.3
11	Migraine	7,768	1.8	637.4
12	Lower respiratory infections	7,585	1.8	622.4
13	Colon and rectum cancers	7,547	1.8	619.3
14	Anxiety disorders	7,439	1.8	610.4
15	Skin diseases	7,011	1.7	575.3
16	Alcohol use disorders	6,677	1.6	547.9
17	Other hearing loss	6,312	1.5	518.0
18	Cirrhosis of the liver	6,218	1.5	510.3
19	Breast cancer	5,915	1.4	485.4
20	Alzheimer disease and other dementias	5,642	1.3	463.0

Global Health Estimates Disability Adjusted Life Years 2000-2021 - UMIC

Upper-middle-income economies

2021				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	**All Causes**	**917,855**	**100.0**	**32563.8**
1	Stroke	79,411	8.7	2817.3
2	COVID-19	74,989	8.2	2660.5
3	Ischaemic heart disease	70,909	7.7	2515.7
4	Back and neck pain	33,465	3.6	1187.3
5	Chronic obstructive pulmonary disease	30,307	3.3	1075.2
6	Diabetes mellitus	29,568	3.2	1049.0
7	Road injury	25,521	2.8	905.5
8	Trachea, bronchus, lung cancers	25,239	2.7	895.4
9	Other hearing loss	19,320	2.1	685.4
10	Depressive disorders	18,150	2.0	643.9
11	Anxiety disorders	16,181	1.8	574.1
12	Migraine	15,625	1.7	554.4
13	Kidney diseases	15,616	1.7	554.0
14	Skin diseases	15,092	1.6	535.4
15	Lower respiratory infections	14,643	1.6	519.5
16	Falls	14,090	1.5	499.9
17	Alzheimer disease and other dementias	14,028	1.5	497.7
18	Interpersonal violence	13,978	1.5	495.9
19	Stomach cancer	13,578	1.5	481.7
20	Cirrhosis of the liver	13,073	1.4	463.8

2000				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	**All Causes**	**790,626**	**100.0**	**33259.2**
1	Stroke	68,290	8.6	2872.8
2	Ischaemic heart disease	47,192	6.0	1985.2
3	Chronic obstructive pulmonary disease	33,996	4.3	1430.1
4	Road injury	30,749	3.9	1293.5
5	Lower respiratory infections	29,428	3.7	1237.9
6	Preterm birth complications	27,988	3.5	1177.4
7	Back and neck pain	23,000	2.9	967.5
8	Congenital anomalies	22,331	2.8	939.4
9	Birth asphyxia and birth trauma	18,681	2.4	785.8
10	Tuberculosis	18,644	2.4	784.3
11	HIV/AIDS	18,490	2.3	777.8
12	Trachea, bronchus, lung cancers	15,519	2.0	652.8
13	Diarrhoeal diseases	15,298	1.9	643.5
14	Interpersonal violence	15,230	1.9	640.7
15	Diabetes mellitus	14,643	1.9	616.0
16	Stomach cancer	14,139	1.8	594.8
17	Cirrhosis of the liver	13,573	1.7	571.0
18	Self-harm	12,822	1.6	539.4
19	Depressive disorders	12,449	1.6	523.7
20	Skin diseases	12,340	1.6	519.1

Global Health Estimates Disability Adjusted Life Years 2000-2021

Lower-middle-income economies

2021				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	All Causes	1,238,335	100.0	41210.0
1	COVID-19	117,831	9.5	3921.2
2	Ischaemic heart disease	74,115	6.0	2466.4
3	Preterm birth complications	60,065	4.9	1998.9
4	Lower respiratory infections	56,921	4.6	1894.3
5	Stroke	48,214	3.9	1604.5
6	Diarrhoeal diseases	45,963	3.7	1529.6
7	Tuberculosis	38,006	3.1	1264.8
8	Birth asphyxia and birth trauma	36,308	2.9	1208.3
9	Chronic obstructive pulmonary disease	33,141	2.7	1102.9
10	Diabetes mellitus	29,485	2.4	981.2
11	Congenital anomalies	27,928	2.3	929.4
12	Malaria	27,865	2.3	927.3
13	Back and neck pain	26,148	2.1	870.2
14	Road injury	25,696	2.1	855.1
15	Iron-deficiency anaemia	21,639	1.7	720.1
16	Depressive disorders	21,363	1.7	710.9
17	Cirrhosis of the liver	20,677	1.7	688.1
18	HIV/AIDS	17,400	1.4	579.1
19	Kidney diseases	16,432	1.3	546.8
20	Migraine	16,409	1.3	546.1

2000				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	All Causes	1,239,930	100.0	58329.5
1	Diarrhoeal diseases	104,269	8.4	4905.1
2	Lower respiratory infections	102,633	8.3	4828.1
3	Preterm birth complications	91,273	7.4	4293.7
4	Tuberculosis	77,363	6.2	3639.4
5	Birth asphyxia and birth trauma	63,607	5.1	2992.2
6	HIV/AIDS	52,926	4.3	2489.8
7	Malaria	41,767	3.4	1964.8
8	Measles	41,625	3.4	1958.2
9	Ischaemic heart disease	38,958	3.1	1832.7
10	Stroke	31,310	2.5	1472.9
11	Other neonatal conditions	27,249	2.2	1281.9
12	Congenital anomalies	23,376	1.9	1099.7
13	Road injury	23,362	1.9	1099.0
14	Iron-deficiency anaemia	20,316	1.6	955.7
15	Neonatal sepsis and infections	20,088	1.6	945.0
16	Chronic obstructive pulmonary disease	19,091	1.5	898.1
17	Protein-energy malnutrition	18,050	1.5	849.1
18	Maternal conditions	17,150	1.4	806.8
19	Cirrhosis of the liver	16,694	1.3	785.3
20	Meningitis	16,493	1.3	775.9

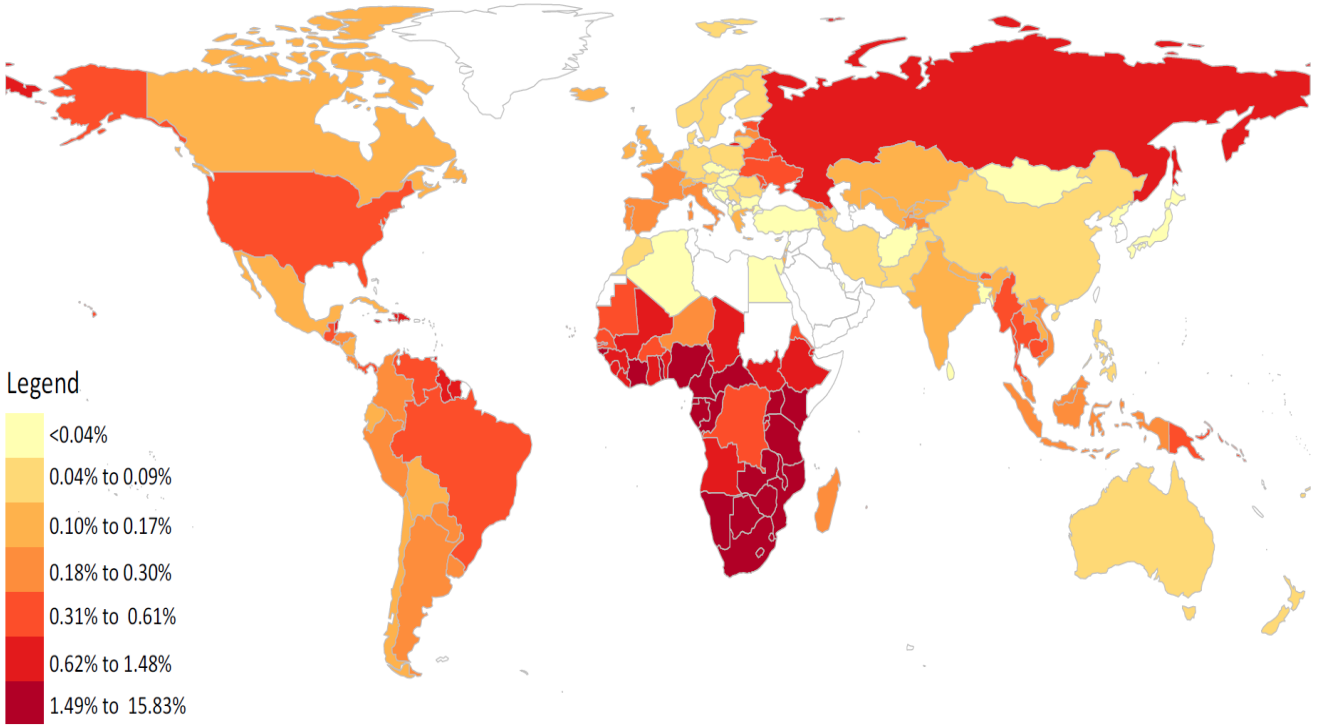
Global Health Estimates Disability Adjusted Life Years 2000-2021

Low-income economies

2021				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	**All Causes**	**350,882**	**100.0**	**50254.2**
1	Lower respiratory infections	27,975	8.0	4006.6
2	Preterm birth complications	25,632	7.3	3671.1
3	Malaria	23,971	6.8	3433.1
4	Diarrhoeal diseases	18,125	5.2	2596.0
5	Birth asphyxia and birth trauma	15,842	4.5	2268.9
6	Tuberculosis	10,795	3.1	1546.1
7	Stroke	10,388	3.0	1487.8
8	COVID-19	9,986	2.8	1430.2
9	HIV/AIDS	9,767	2.8	1398.9
10	Road injury	9,130	2.6	1307.7
11	Ischaemic heart disease	8,525	2.4	1221.0
12	Collective violence and legal intervention	8,450	2.4	1210.3
13	Congenital anomalies	8,200	2.3	1174.5
14	Other neonatal conditions	6,148	1.8	880.6
15	Maternal conditions	5,719	1.6	819.1
16	Measles	5,711	1.6	817.9
17	Back and neck pain	5,378	1.5	770.2
18	Meningitis	5,342	1.5	765.1
19	Depressive disorders	5,083	1.4	728.1
20	Protein-energy malnutrition	4,832	1.4	692.1

2000				
Rank	Cause	DALYs (000s)	% DALY	DALYs per 100,000
0	**All Causes**	**375,262**	**100.0**	**96201.2**
1	Lower respiratory infections	39,693	10.6	10175.7
2	Malaria	35,396	9.4	9074.0
3	Diarrhoeal diseases	31,974	8.5	8196.7
4	HIV/AIDS	26,998	7.2	6921.0
5	Preterm birth complications	25,157	6.7	6449.3
6	Measles	21,547	5.7	5523.7
7	Tuberculosis	19,161	5.1	4912.2
8	Birth asphyxia and birth trauma	16,122	4.3	4133.0
9	Protein-energy malnutrition	10,186	2.7	2611.3
10	Meningitis	9,195	2.5	2357.2
11	Road injury	7,160	1.9	1835.6
12	Maternal conditions	7,074	1.9	1813.4
13	Stroke	6,980	1.9	1789.4
14	Collective violence and legal intervention	6,776	1.8	1737.1
15	Other neonatal conditions	6,361	1.7	1630.6
16	Ischaemic heart disease	5,124	1.4	1313.5
17	Congenital anomalies	5,061	1.3	1297.4
18	Neonatal sepsis and infections	4,888	1.3	1253.0
19	Whooping cough	4,674	1.2	1198.2
20	Cirrhosis of the liver	2,927	0.8	750.3

What is the global burden of ASCVD due to HIV?



Population attributable risk of HIV for ASCVD by country

Shah et al, Circulation, 2018

RESEARCH ARTICLE Open Access

Causes of hospitalisation among a cohort of people with HIV from a London centre followed from 2011 to 2018

Sophia M. Rein[1*], Fiona C. Lampe[1], Clinton Chaloner[1], Adam Stafford[2], Alison J. Rodger[1], Margaret A. Johnson[2], Jeffrey McDonnell[1], Fiona Burns[1,2], Sara Madge[2], Alec Miners[4], Lorraine Sherr[1], Simon Collins[3], Andrew Speakman[1], Andrew N. Phillips[1] and Colette J. Smith[1]

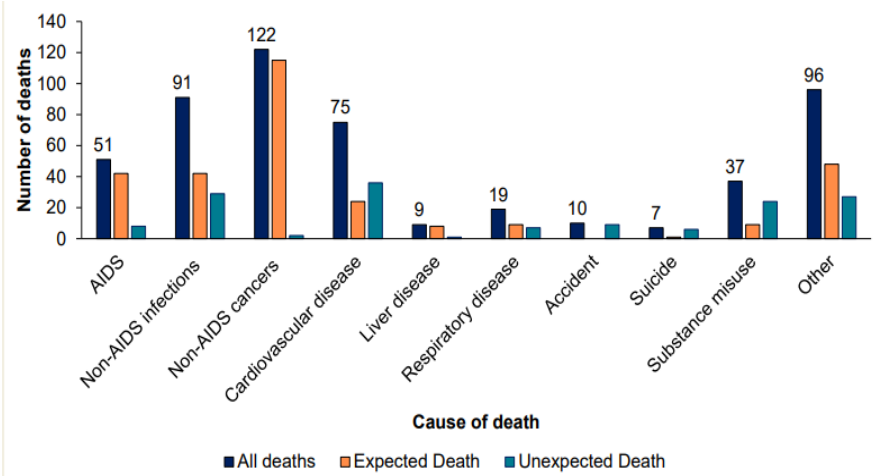


Figure 2. Cause of death among people with HIV by whether the death was expected: UK, 2021

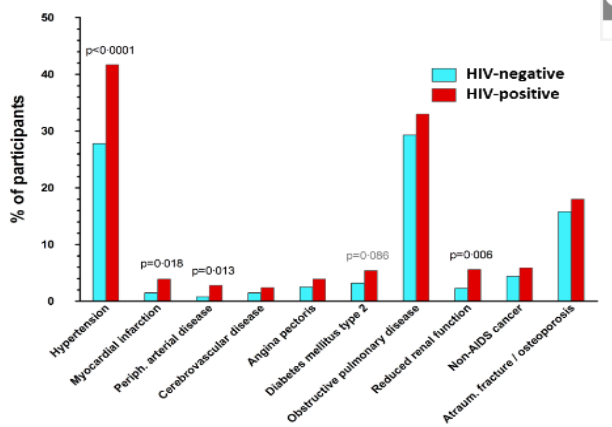
Hospitalization Rates and Causes Among Persons With HIV in the United States and Canada, 2005–2015 FREE

Thibaut Davy-Mendez, Sonia Napravnik, Brenna C Hogan, Keri N Althoff, Kelly A Gebo, Richard D Moore, Michael A Horberg, Michael J Silverberg, M John Gill, Heidi M Crane ...
Show more

The Journal of Infectious Diseases, Volume 223, Issue 12, 15 June 2021, Pages 2113–2123,

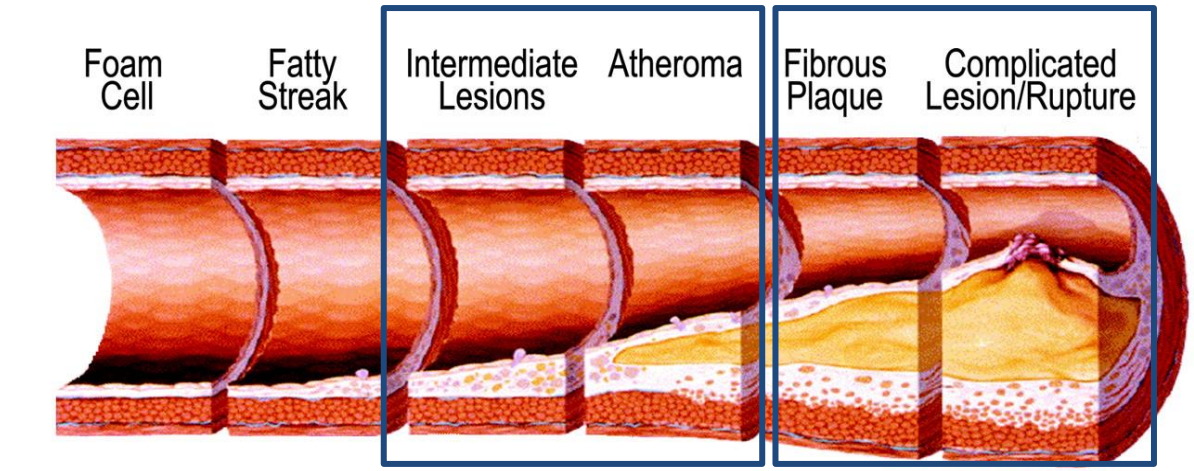
Front. Public Health, 08 November 2022
Sec. Infectious Diseases: Epidemiology and Prevention
Volume 10 - 2022 | https://doi.org/10.3389/fpubh.2022.1000942

Trends in rates and causes of hospitalization among people living with HIV in the antiretroviral therapy era: A retrospective cohort study in China, 2008–2020



Judith Schouten et al. Clin Infect Dis. 2014;59:1787-1797

Inflammation and immune activation can drive ASCVD risk



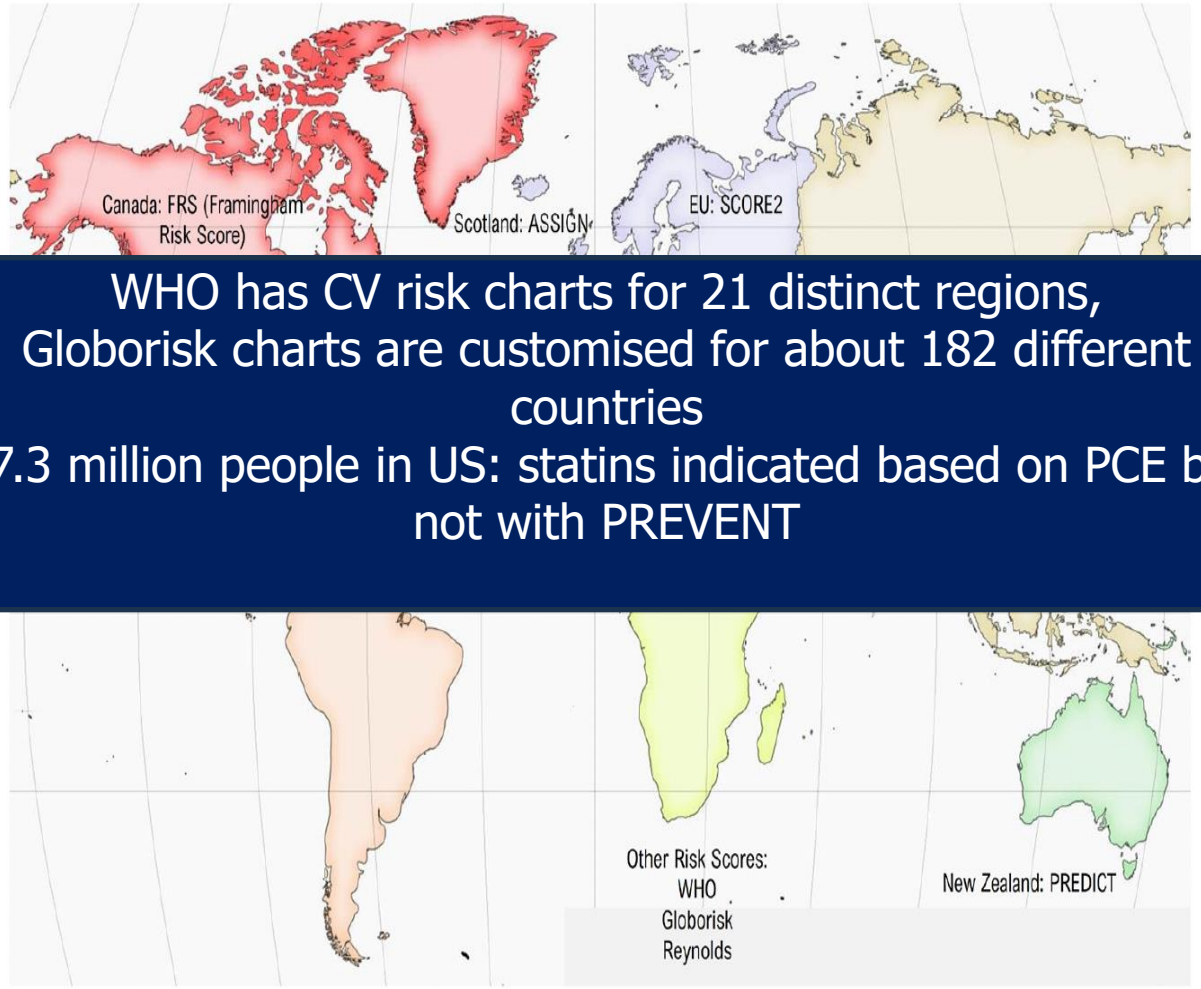
1°& Messenger Inflamm. Cyto/Chemokines		Cellular Adhesion Molecules	Plaque Destabilization		Plaque Rupture
IL-1	IL-6*	sICAM	IL-18*	MPO*	PAPP-A*
TNF-α	IL-18*	sVCAM	oxLDL*	MMPs *	sCD40L*
	MCP-1*	sSelectins	Lp-PLA$_2$*	MCP-1*	
			GPx-1*	PlGF*	

Acute Phase Reactants

CRP*, sPLA$_2$*, SAA, Fibrinogen, WBCC

Koenig et al, ATVB 2007

CV Risk prediction score tools used globally



WHO has CV risk charts for 21 distinct regions,
Globorisk charts are customised for about 182 different countries
17.3 million people in US: statins indicated based on PCE but not with PREVENT

Heart 2023 Nov 2:heartjnl-2023-322928
JAMA Int Med 2024 jun 10

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2022 Jan 6.
Published in final edited form as:
Curr HIV/AIDS Rep. 2021 Aug; 18(4): 271–279.
Published online 2021 Jul 11. doi: 10.1007/s11904-021-00567-w

PMCID: PMC8733948
NIHMSID: NIHMS1763687
PMID: 34247329

Assessing Cardiovascular Risk in People Living with HIV: Current Tools and Limitations

Amit C. Achhra,[1] Asya Lyass,[2] Leila Borowsky,[3] Milana Bogorodskaya,[4] Jorge Plutzky,[5] Joseph M. Massaro,[2] Ralph B. D'Agostino, Sr.,[2] and Virginia A. Triant[1,3]

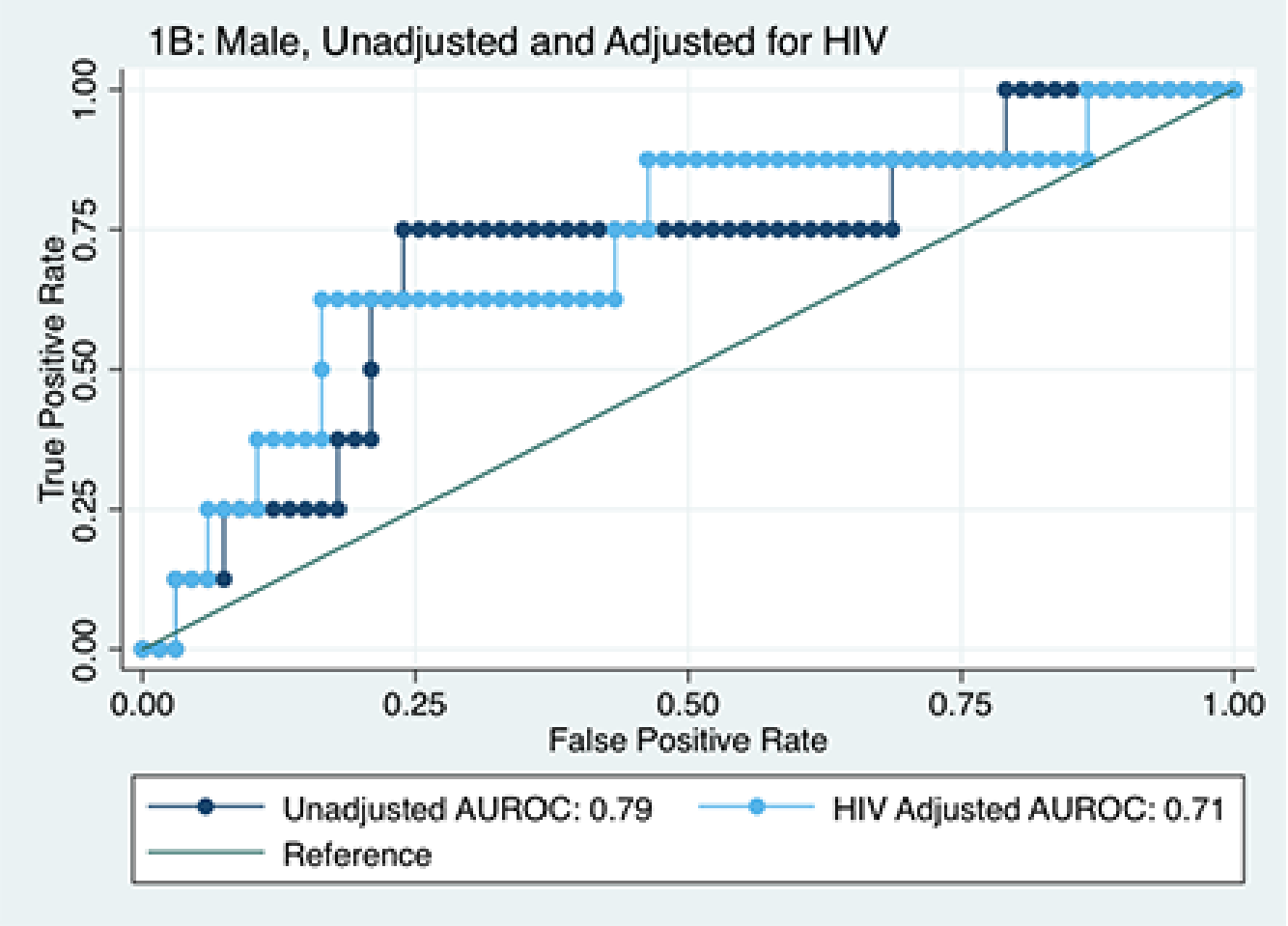
In validation studies in cohorts of PLWH, these models generally **underestimate** CVD risk, **especially in individuals who are younger, women, Black race or predicted to be at low/intermediate risk**

An HIV-specific CVD prediction model, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) model, is available, but its performance is modest, especially in US-based cohorts

Enhancing CVD prediction with novel biomarkers of inflammation or coronary artery calcification is of interest but has not yet been evaluated in PLWH

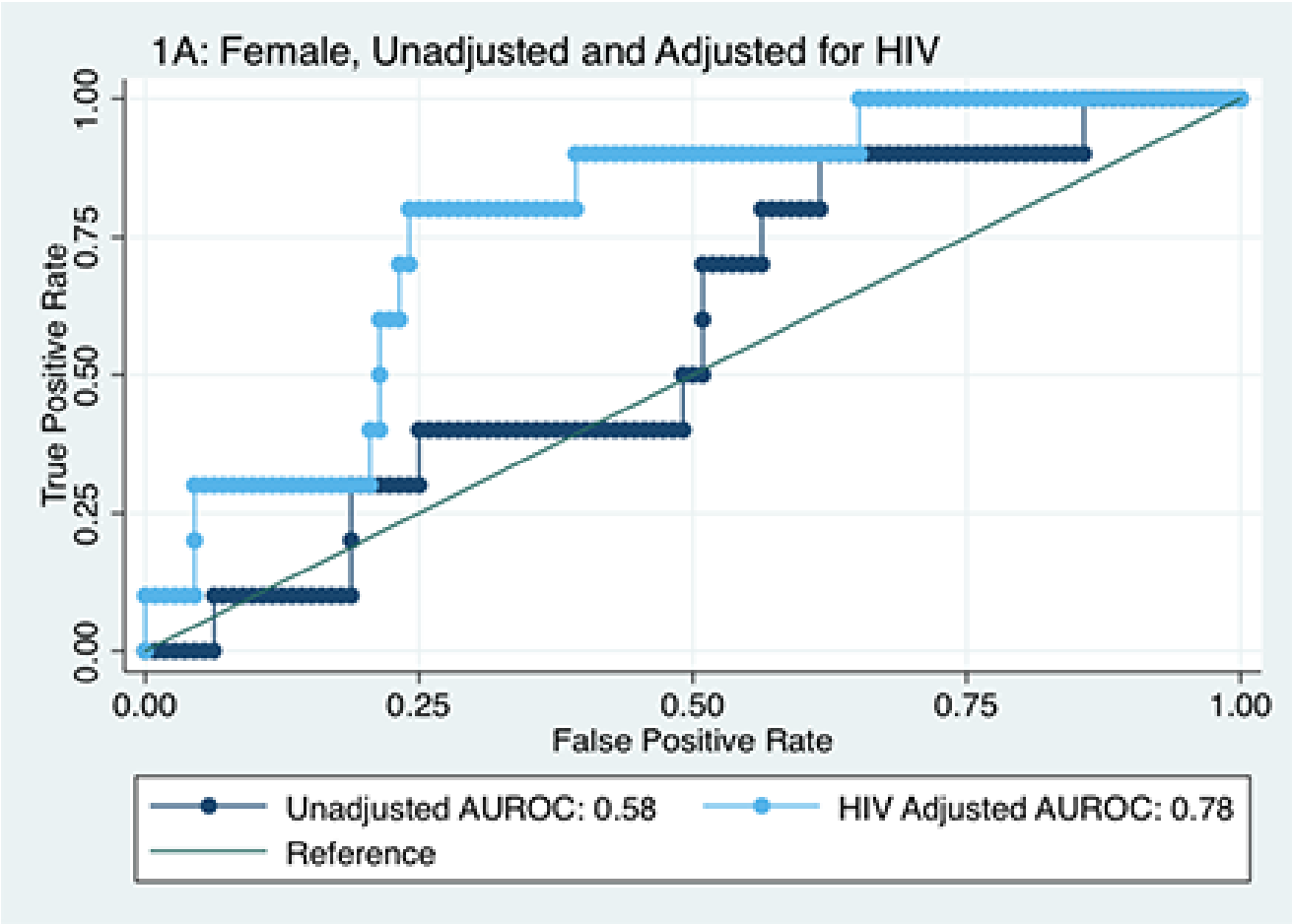
Studies on CVD risk prediction are lacking in diverse PLWH globally
Risk discussion and prediction functions tailored to PLWH in diverse settings will enhance clinicians' ability to deliver optimal preventive care.

ASCVD risk as predictor of CAC– Men



Kentoffio et al, Int J Cardiol CV Risk Prev 2022

ASCVD risk as predictor of CAC– Women



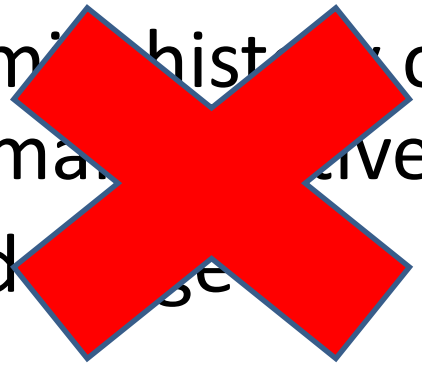
Kentoffio et al, Int J Cardiol CV Risk Prev 2022

Interventions to improve cardiovascular risk

- Smoking cessation
- Regular exercise
- High blood pressure
- Diabetes
- Overweight or obesity
- Family history of heart disease, especially before the age of 55 in male relatives or before 65 in female relatives
- Older age

Interventions to improve cardiovascular risk

- Smoking cessation
- Regular exercise
- High blood pressure
- Diabetes
- Overweight or obesity
- Family history of heart disease, especially before the age of 55 in male relatives or before 65 in female relatives
- Old age



Smoking cessation: Switch study!

Self discipline
Lifelong!

Government intervention
Ban in public places
Age limits

Smoking cessation
Medication side effects

- **Bupropion**
  - Dry mouth
  - Problems sleeping. Stop taking this medicine right away if you have changes in behavior. These include anger, agitation, depressed mood, thoughts of suicide, or attempted suicide.

- **VARENICLINE (CHANTIX)**
  - Headaches, problems sleeping, sleepiness, and strange dreams.
  - Constipation, intestinal gas, nausea, and changes in taste.
  - Depressed mood, thoughts of suicide and attempted suicide. Call your provider right away if you have any of these symptoms.
  - **NOTE: Use of this medicine is linked to an increased risk of heart attack and stroke!!!**

- **OTHER MEDICINES**
  - The benefits are much less consistent, so they are considered second-line treatment.
  - Clonidine is normally used to treat high blood pressure. It may help when it is started before quitting. This drug comes as a pill or patch.
  - Nortriptyline is another antidepressant. It is started 10 to 28 days before quitting.

Perceived barriers to and facilitators for regular exercise

- Design of the exercise programme
  - Individualisation
  - Length of programme
- Social support
- Self-efficacy
- Integration into daily living
- Presence of an MDT
- Supervision during sessions
- Use of Technology
- Participant education
- Presence of pleasant and unpleasant experiences
- Communication and feedback
- Participant's active role
- Goal setting

Collado-Mateo, et al. Int J Environ Res Public Health 2021, Pavey et al., 2012; Picorelli et al., 2014

Perceived barriers to and facilitators for exercise

- Design of the exercise programme
  - Individualisation
  - Length of programme
- Social support
- Self-efficacy
- Integration into daily living
- Presence of an MDT
- Supervision during sessions
- Use of Technology
- Participant education
- Presence of pleasant and unpleasant experiences
- Communication and feedback
- Participant's active role
- Goal setting

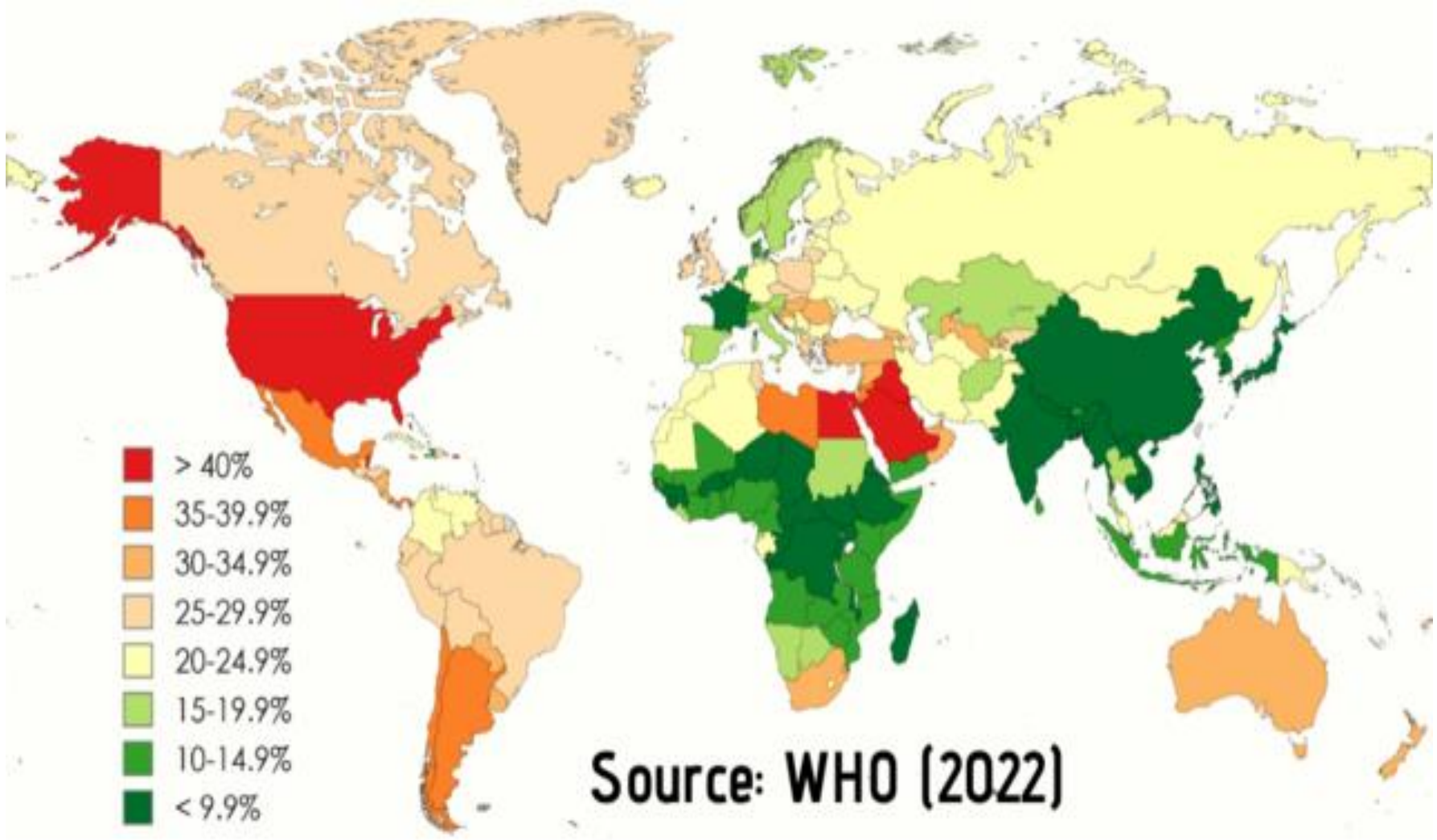
- Systematic review
- Programme completion 65% to 86%
- Sessions attended fluctuated from 58% to 77%
- The average number of home exercise sessions completed per week ranged from 1.5 to 3 times per week

Collado-Mateo, et al. Int J Environ Res Public Health 2021, Pavey et al., 2012; Picorelli et al., 2014

Interventions to improve cardiovascular risk

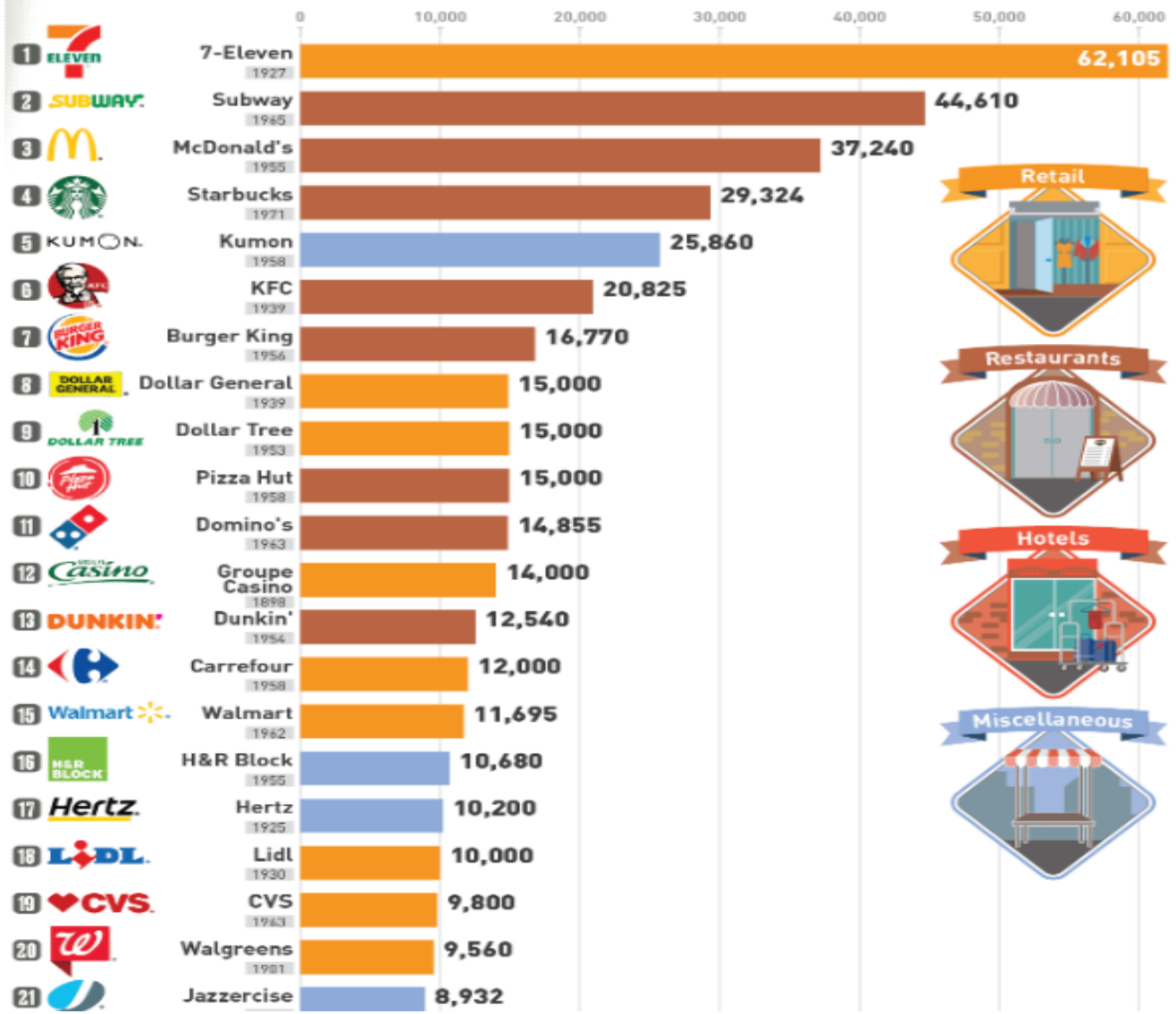
- Smoking cessation
- Regular exercise
- High blood pressure
- Diabetes
- Overweight or obesity
- Family history of heart disease, especially before the age of 55 in male relatives or before 65 in female relatives
- Older age

Obesity epidemic expected to worsen



WHICH BUSINESSES HAVE THE MOST PHYSICAL LOCATIONS AROUND THE WORLD?

KEY
Franchise name
Year founded

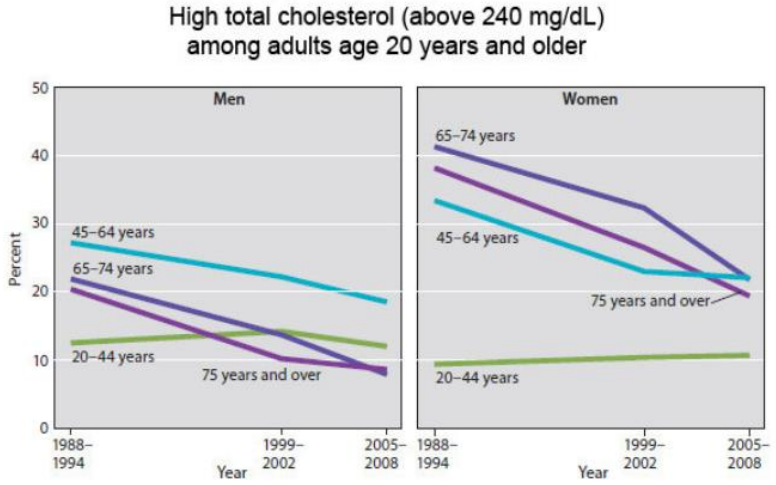


Example of the US

- Half of men, ages to 65 to 74, and 39% of women, ages 75 and older take statins
- Combine the 45+ age groups and both genders, and it comes out that one in four Americans, ages 45 and older, are taking a statin
- There are roughly 127 million Americans over age 45
- Based on the last government health survey almost 32 million Americans take a statin
- That’s the equivalent of the entire populations of Florida and Illinois combined.

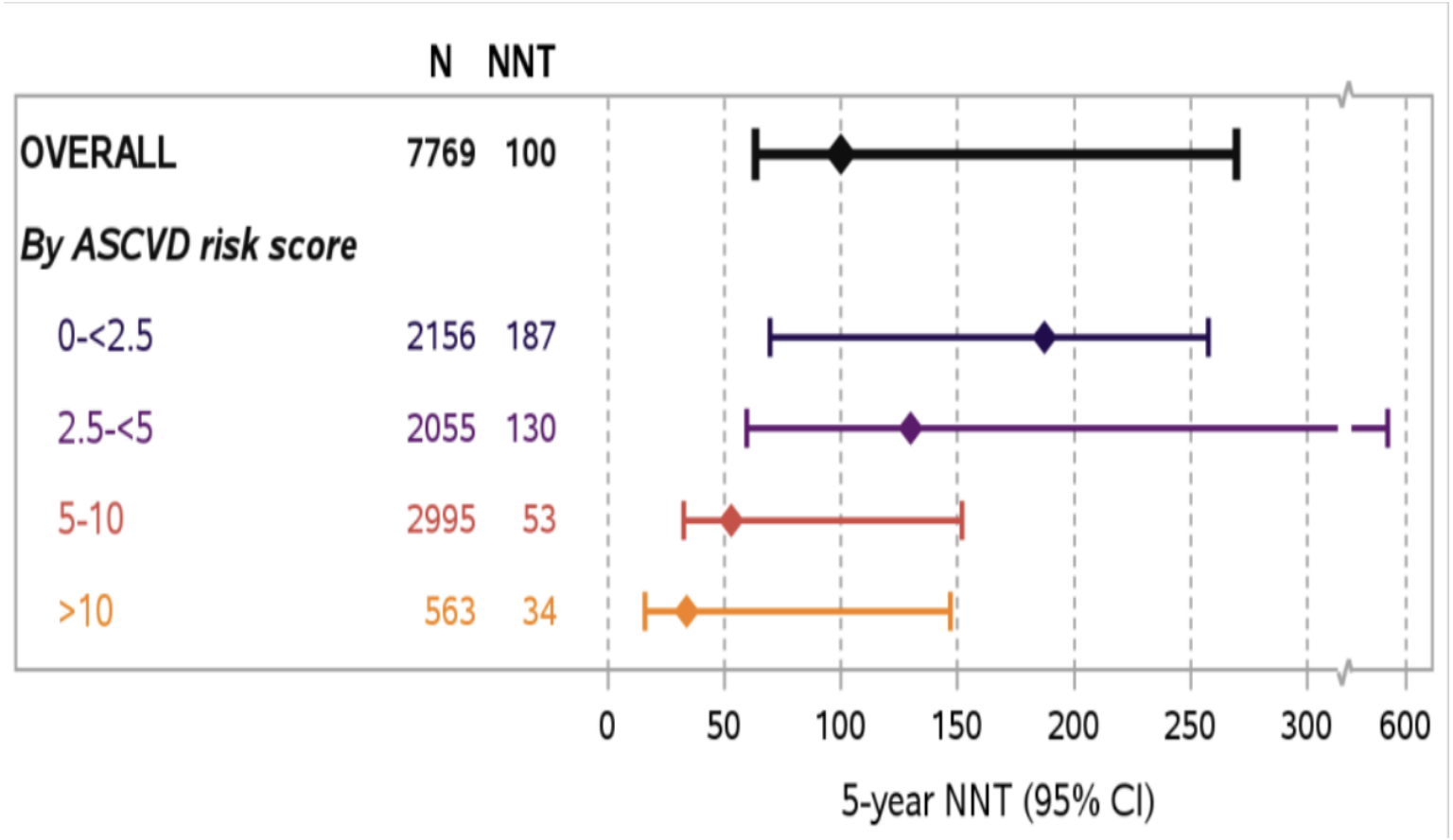
Example of the US

- Half of men, ages to 65 to 74, and 39% of women, ages 75 and older take statins
- Combine the 45+ age groups and both genders, and it comes out that one in four Americans, ages 45 and older, are taking a statin
- There are roughly 127 million Americans over age 45
- Based on the last government health survey almost 32 million Americans take a statin



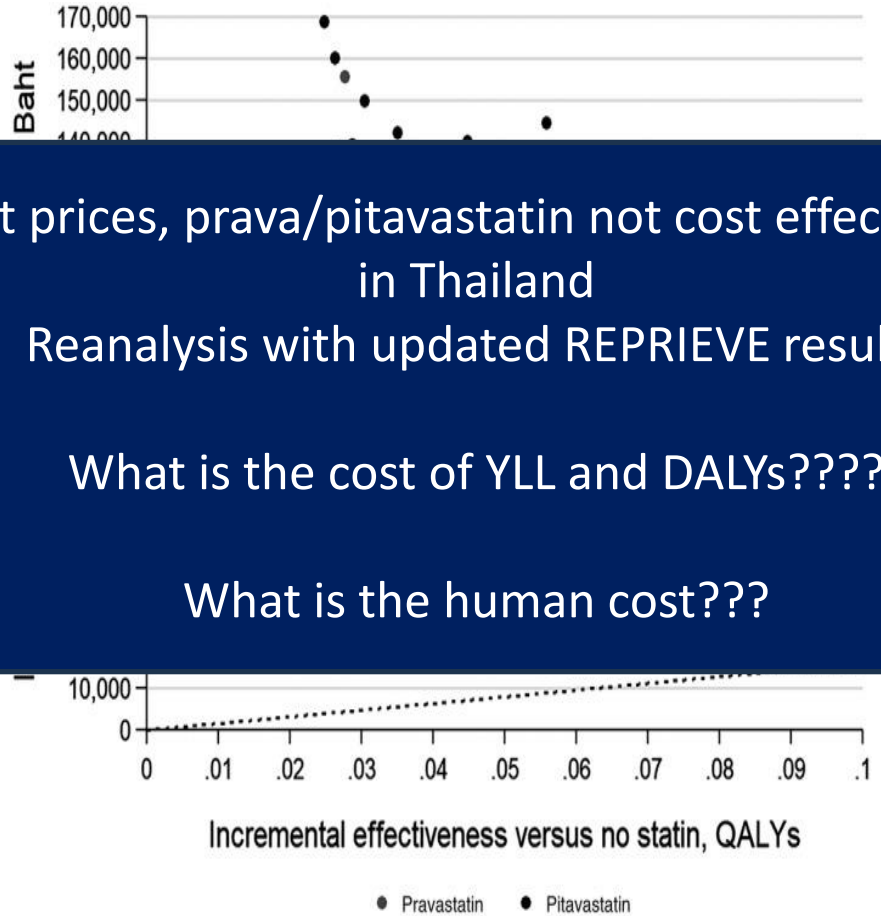
Over 30 years of experience of statin use in general population
Myositis minimal in reality
Diabetes is not caused by statins but may cause early expression of preexisting risk by 1-2 yrs

NNT_5 in REPRIEVE



N Engl J Med 2024;390:1626-1628

Cost effectiveness modelling



At current prices, prava/pitavastatin not cost effective for PWH in Thailand

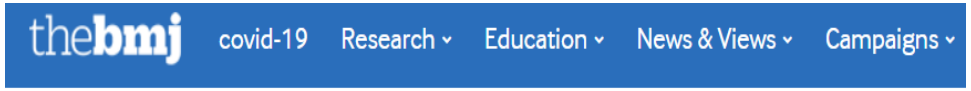
Reanalysis with updated REPRIEVE results

What is the cost of YLL and DALYs????

What is the human cost???

J Intl AIDS Soc 2020 Jun; 23(Suppl 1): e25494

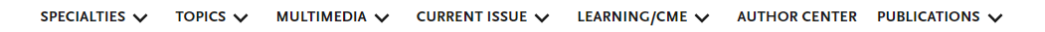
Other HIV studies stopped early



News

HIV trial stopped early after good results

BMJ 1997 ; 314 doi: https://doi.org/10.1136/bmj.314.7082.695l (Published 08 March 1997)
Cite this as: *BMJ* 1997;314:695

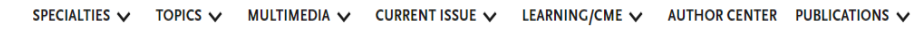


ORIGINAL ARTICLE

CD4+ Count–Guided Interruption of Antiretroviral Treatment

Author: The Strategies for Management of Antiretroviral Therapy (SMART) Study Group* Author Info & Affiliations

Published November 30, 2006 | N Engl J Med 2006;355:2283-2296 | DOI: 10.1056/NEJMoa062360
VOL. 355 NO. 22



ORIGINAL ARTICLE

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

Author: The INSIGHT START Study Group Author Info & Affiliations

Published August 27, 2015 | N Engl J Med 2015;373:795-807 | DOI: 10.1056/NEJMoa1506816 | VOL. 373 NO. 9

ARTICLES · Volume 387, Issue 10013, P53-60, January 02, 2016 · *Open Access* Download Full Issue

Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial

Prof Sheena McCormack, MSc [a,o,†] · Prof David T Dunn, PhD [a,†] · Monica Desai, MPH [a,b] · David I Dolling, MSc [a] · Mitzy Gafos, PhD [a] · Richard Gilson, MD [c,r] · et al. Show more

No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY

29 June 2020

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on lopinavir-ritonavir, 29 June 2020

ORIGINAL ARTICLE

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Authors: Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Trii Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., +19, for the REPRIEVE Investigators* Author Info & Affiliations

Published July 23, 2023 | N Engl J Med 2023;389:687-699 | DOI: 10.1056/NEJMoa2304146 | VOL. 389 NO. 8

Current recommendations

	DHHS 2024	EACS 2024	BHIVA 2024
Screening tool	PCE	SCORE2 & SCORE2-OP	QRISK
CV risk ≥ 10%	Recommend (A1)	Indicated	Recommend (prioritized)
CV risk 5%-<10%	Recommend (A1)	Recommend	Recommend (prioritized)
CV risk < 5%	Consider (C1) • Account for HIV related factors	Consider • Evaluate risk & benefits • Informed decision	Recommend
Other factors	• Shared decision	• Shared decision • Individualized approach	Combined holistic approach

Summary why should we treat all people living with HIV above 40 years with a statin?

- The REPRIEVE trial showed that pitavastatin treatment lowers the risk of adverse cardiovascular events among individuals with HIV and low-to-moderate risk of cardiovascular disease.
- Causes of hospitalizations amongst PWH, YLL, DALYs globally due to MACE are increasing
- Cost-benefit analysis of statins doesn't include YLL and DALYs
- Human cost???
- High adherence and consistent monitoring – we do that anyway
- Drug drug interactions – we check that anyway
- WOMEN!!!!!
- Holisitic approach IS important
- BUT
- MAKE EVERY CONTACT COUNT


YES!
YES!!
YES!!