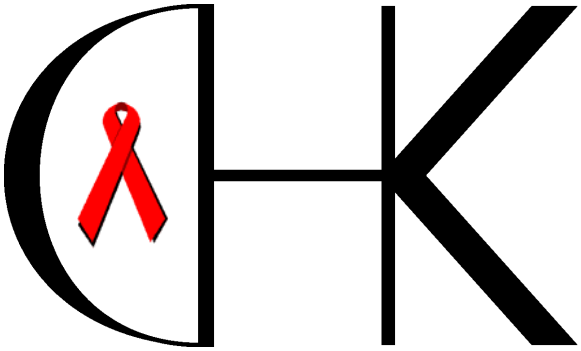
DEN DANSKE HIV KOHORTE



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Oktober 2007

Indholdsfortegnelse

Forord

Nærværende rapport er en status over Den Danske HIV Kohortes arbejde frem til sommeren 2007. Starten på 2007 har været præget af, at Den Danske HIV Kohorte er flyttet fysisk fra Infektionsmedicinsk Forskningsenhed på Odense Universitetshospital til Epidemiklinikken, Rigshospitalet. Kohorten har efterhånden fået en størrelse der gør, at en flytning er en omfangsrig manøvre. Specielt hjælp fra Ann Brit Eg Hansen og Winne Bergsted har gjort processen problemfri. Jeg vil gerne takke Medicinsk Center, Odense Universitetshospital for gode arbejdsforhold, under kohortens ophold på hospitalet og for det gode samarbejde, der har været med Medicinsk Afdeling C og Infektionsmedicinsk Forskningsenhed .

Rapporten fokuser på overordnede resultater. Af hensyn til ønsker fra industrien er der dog til slut i den udvidede rapport medtaget mere specifikke beregninger over de enkelte præparaters anvendelsesmønstre i Danmark. Visse præparater og forhold, som stort set ikke har ændret sig det sidste år, er ikke medtaget, og der henvises i stedet til rapporterne for 2004, 2005 og 2006.

Data er baseret på de tilgængelige opdateringer i august 2007. Epidemiologiske opgørelser er ikke virkeligheden, men et spejlbillede heraf. Resultaterne i nærværende rapport er derfor heller ikke bedre end de indgåede data.

Jeg vil endnu engang benytte lejligheden til at takke DHKs styregruppe, de trofast arbejdende forskningssygeplejersker og de enkelte centre og deres afdelingsledelser for et gnidningsfrit samarbejde.

Den Danske HIV Kohorte er helt afhængig af ekstern støtte. I den forbindelse vil jeg specielt takke AIDS Fondet, Patientcenter Blå - Odense Universitets Hospital, Klinisk Institut – Syddansk Universitet, Apotekerfonden, Fyns Amts Forskningspulje og Preben and Anna Simonsens Fond. Følgende firmaer har gjort aktuelle årsrapport mulig: GlaxoSmithKline, Bristol Myers Squibb, Merck-Sharp-Dohme, Boeringer Ingelheim og Tibotec/Janssen-Cilag.

Tallene i rapporten er ikke kvalitetssikrede i samme grad som for de videnskabelige publikationer, som udgår fra databasen. Der tages derfor forbehold for eventuelle regnefejl i rapporten.

Rapporten foreligger i to udgaver. En koncentreret form og en udvidet rapport, som inkluderer data om de enkelte antivirale præparater. I den udvidede udgave er i sidste sektion inkluderet udvalgte publikationer fra Den Danske HIV Kohorte. Der er i visse tabellers anført et tal med nummer (f. eks. B7), det er henvisninger til tabeller i Den Danske HIV Kohortes database, og er kun til internt brug for personalet ved kohorten.

Niels Obel

Den Danske HIV Kohortes opbygning.

Tilknyttede videnskabelige medarbejdere

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Sygeplejerskerne Iben Rose Loftheim, Inge Bossen og Lotte Rodkjær, Skejby Sygehus

Sygeplejerske Dina Brændgård Børgesen, Aalborg Sygehus

Sygeplejerske Lene Kræmer, Fredericia & Kolding Sygehus

Sygeplejerske Jaqueline Hjertstedt, Helsingør Sygehus

Sygeplejerske Ellen Christensen, og sekretær Ulla Overgaard, Herning Regionshospital

Arbejder udgået fra Den Danske HIV Kohorte

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Demografi

Antal patienter i Den Danske HIV Kohorte (G2)	**5.055**
Heraf indgår følgende i:	
Den grønlandske kohorte (G1a)	**124**
Den Danske Børne HIV Kohorte (positiv HIV test før 16 år) (B4)	**104**
Antal patienter, som er startet på HAART (G10)	**3.568**
Antal virologiske målinger i DHK (B2)	**96.664**
Antal CD4 målinger i DHK (B3)	**110.271**
Antal initieringer af antiretroviral behandling og behandlingsskift registreret i DHK (B1)	**15.953**

Tidspunkt for første HIV positiv (ikke grønlandske patienter)

Årstal	Antal patienter (B5)	Heraf sat i behandling indenfor et år (G12)
1994 eller tidligere	2062	0 (0,0%)
1995	273	18 (6,6%)
1996	233	97 (41,6%)
1997	245	128 (52,2%)
1998	208	111 (53,4%)
1999	248	139 (56,0%)
2000	231	136 (58,9%)
2001	286	175 (61,2%)
2002	233	135 (57,9%)
2003	205	121 (59,0%)
2004	258	125 (48,4%)
2005	197	99 (50,3%)
2006	186	*
Ukendt	29	

*Danner først mening ved udgangen af 2007.

Dødsfald blandt HIV positive fordelt på år (G7)

Årstal	Antal patienter
1995	251
1996	167
1997	88
1998	62
1999	84
2000	52
2001	73
2002	61
2003	75
2004	80
2005	67
2006	53
I alt (efter31/12-1994)	**1113**

Samlede antal HIV positive patienter set ved centrene (G1)

Centre	Antal patienter	Procentvis fordeling
Uden center/andre centre	15	0,3 %
Herning	92	1,9 %
Helsingør	76	1,5 %
Hvidovre	1814	36,8 %
Hvidovre børneafdelingen	42	0,9 %
Kolding	69	1,4 %
Odense	402	8,2 %
Odense-børneafd.	8	0,2 %
Rigshospitalet	1641	33,3 %
Skejby børneafdelingen	14	0,3 %
Skejby voksenafdelingen	556	11,3 %
Aalborg	201	4,1 %
I alt	4930	100 %

Antal HIV positive patienter set ved centrene med sidste ambulant kontrol efter 1. januar 2003 (G3)

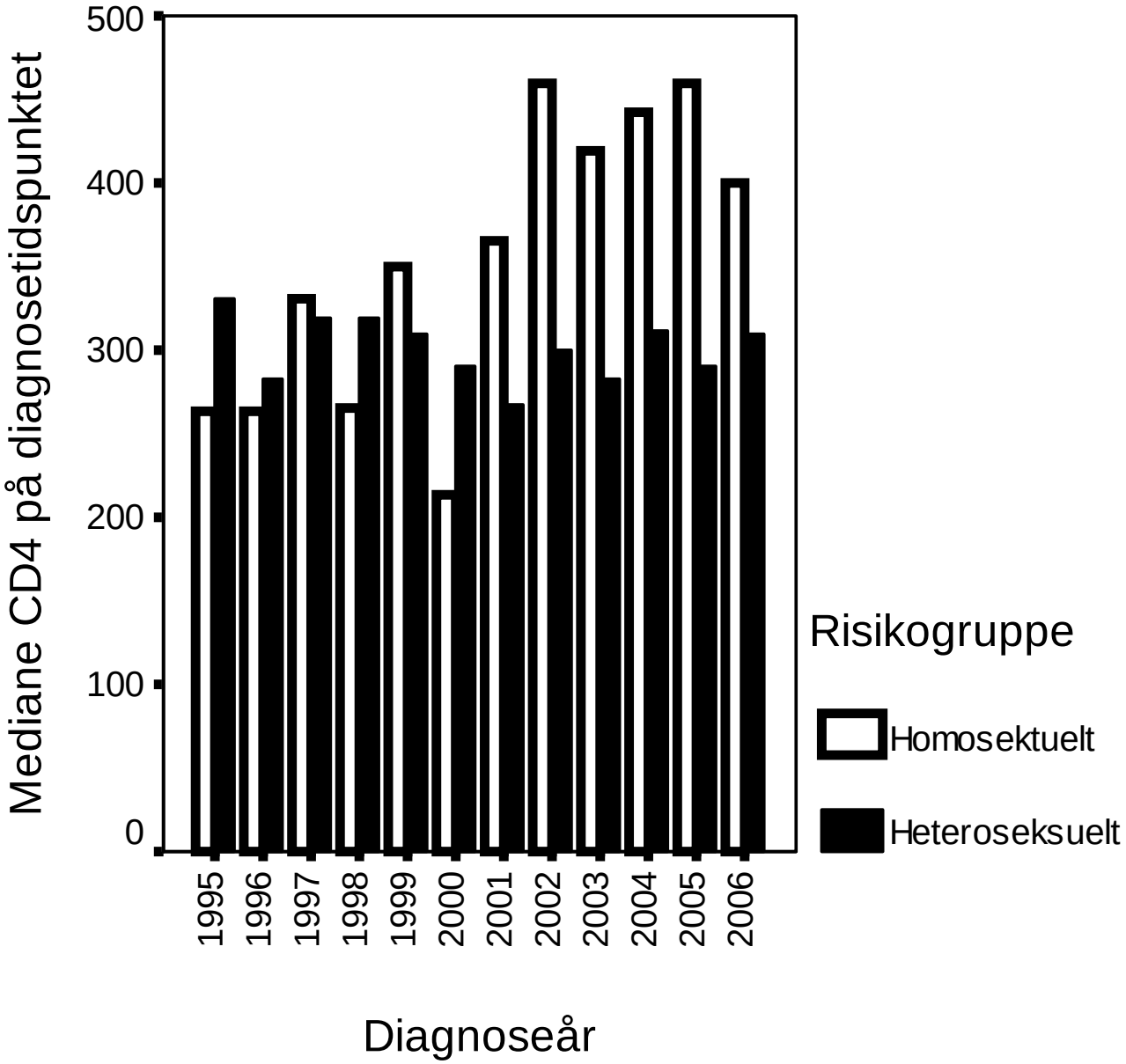
Centre	Antal patienter	Procentvis fordeling
Andre centre	8	0,2 %
Herning	83	2,2 %
Helsingør	73	1,9 %
Hvidovre	1352	35,1 %
Hvidovre børneafdelingen	36	0,9 %
Kolding	62	1,6 %
Odense	314	8,2 %
Odense –børneafd.	6	0,2 %
Rigshospitalet	1276	33,1 %
Skejby børneafdelingen	14	0,4 %
Skejby voksenafdelingen	453	11,8 %
Aalborg	174	4,5 %
I alt	3851	100 %

Første HIV positiv fordelt på køn og år for HIV positiv (B6)

År for HIV positiv	Mænd	%	Kvinder	%
1994 eller tidligere	1655	80,3	407	19,7
1995	204	74,8	69	25,3
1996	172	73,8	61	26,2
1997	182	74,0	63	25,7
1998	151	72,6	57	27,4
1999	154	62,3	93	37,7
2000	152	65,8	79	34,2
2001	188	65,7	98	34,3
2002	153	65,7	80	34,3
2003	154	75,1	51	24,9
2004	192	74,4	66	25,6
2005	149	75,6	48	24,4
2006	131	70,8	54	29,2
2007	27	75,0	9	25,0

Smittemåde fordelt på år for HIV positiv (B7)

	Homoseksuel	Heteroseksuel	I.V stofmisbrug	Hæmofili og blodtransfusion	Perinatalt	Andet/ukendt
1994 eller tidligere	1087 (52,8%)	500 (24,3%)	319 (15,5%)	59 (2,9%)	28 (1,4%)	65 (3,2%)
1995	111 (40,7%)	114 (41,8%)	24 (8,8%)	3 (1,1%)	3 (1,1%)	18 (6,6%)
1996	90 (38,6%)	100 (42,9%)	20 (8,6%)	4 (1,7%)	4 (1,7%)	15 (6,5%)
1997	91 (37,3%)	113 (46,3%)	19 (7,8%)	2 (0,8%)	5 (2,0%)	14 (5,8%)
1998	79 (38,0%)	93 (44,7%)	19 (9,1%)	1 (0,5%)	6 (2,9%)	10 (4,8%)
1999	80 (32,4%)	128 (51,8%)	18 (7,3%)	3 (1,2%)	1 (0,4%)	17 (6,9%)
2000	70 (30,3%)	127 (55,0%)	16 (6,9%)	4 (1,7%)	5 (2,2%)	9 (3,9%)
2001	86 (30,3%)	148 (52,1%)	27 (9,5%)	0 (0,0%)	9 (3,2%)	14 (4,9%)
2002	76 (32,6%)	118 (50,6%)	21 (9,0%)	3 (1,3%)	5 (2,1%)	10 (4,3%)
2003	81 (40,1%)	81 (40,1%)	22 (10,9%)	0 (0,0%)	2 (1,0%)	16 (7,9%)
2004	124 (48,1%)	106 (41,1%)	13 (5,1%)	2 (0,8%)	4 (1,6%)	9 (3,5%)
2005	96 (48,7%)	78 (39,6%)	13 (6,6%)	1 (0,5%)	3 (1,5%)	6 (3,0%)
2006	80 (43,0%)	84 (45,2%)	9 (4,8%)	0 (0,0%)	0 (0,0%)	13 (7,0%)



Mediane CD4 på diagnosetidspunktet, fordelt på risikogruppe.

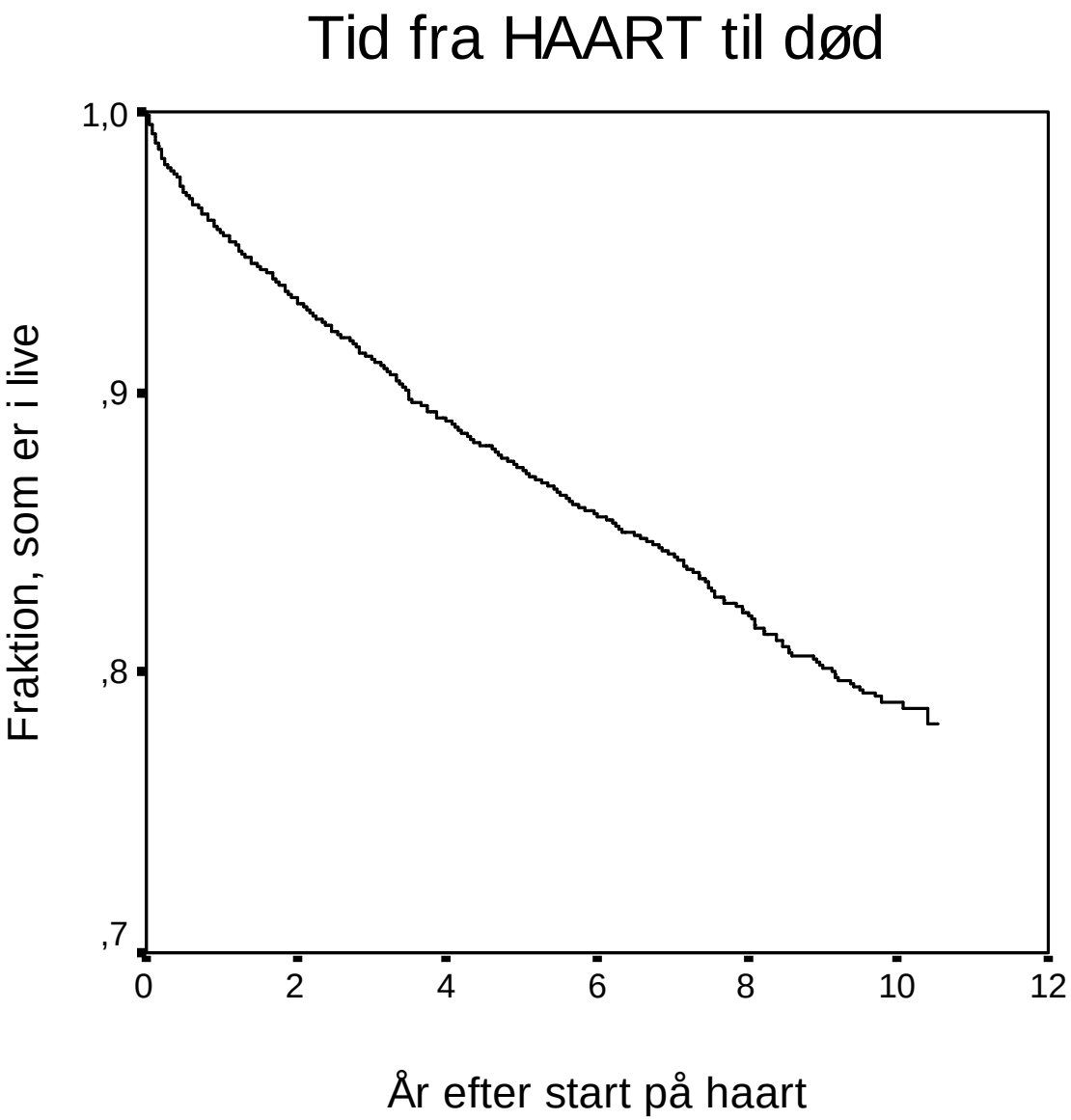
Behandlingsdata

Antal patienter, som starter HAART fordelt på årstal (G8)

Årstal	Antal
1994	6
1995	34
1996	494
1997	751
1998	314
1999	302
2000	266
2001	297
2002	239
2003	215
2004	239
2005	186
2006	188

Antal patienter, som årligt skifter behandling (G14)

Årstal	Antal
1995	3
1996	171
1997	531
1998	628
1999	791
2000	730
2001	809
2002	768
2003	825
2004	788
2005	1112
2006	887


Tid fra HAART til død
Fraktion, som er i live
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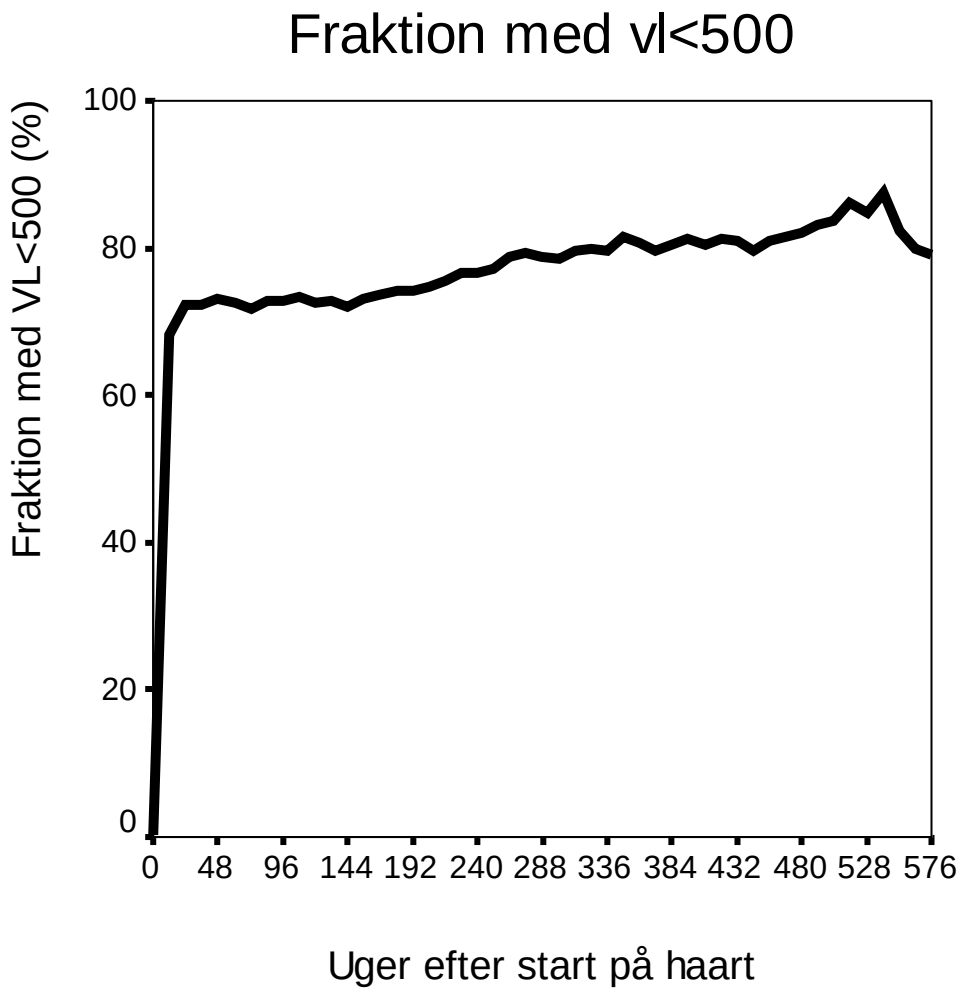
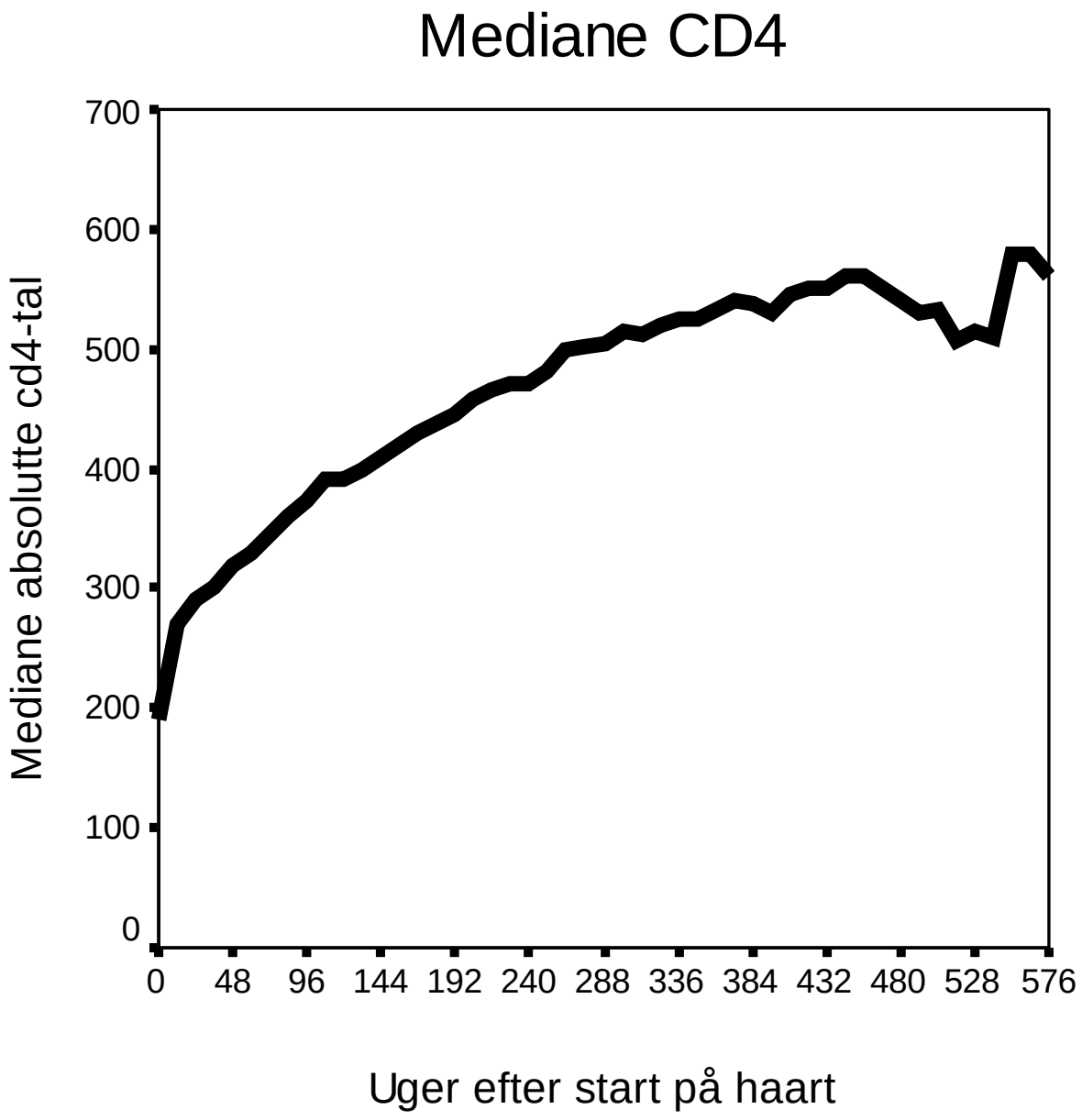
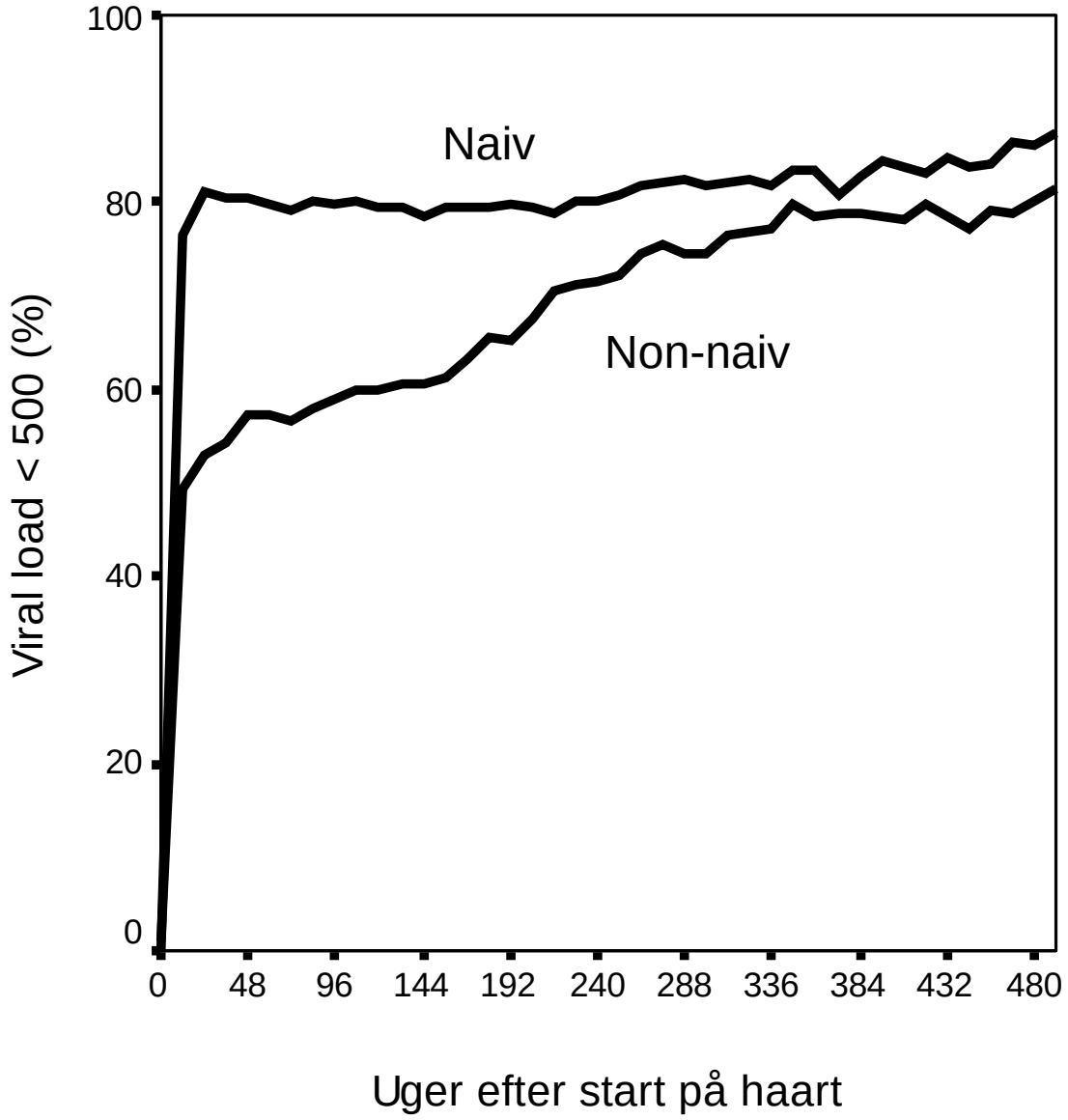
År efter start på haart



Viser fraktionen af patienter, som har et viral load < 500 fordelt på uger efter start af HAART.



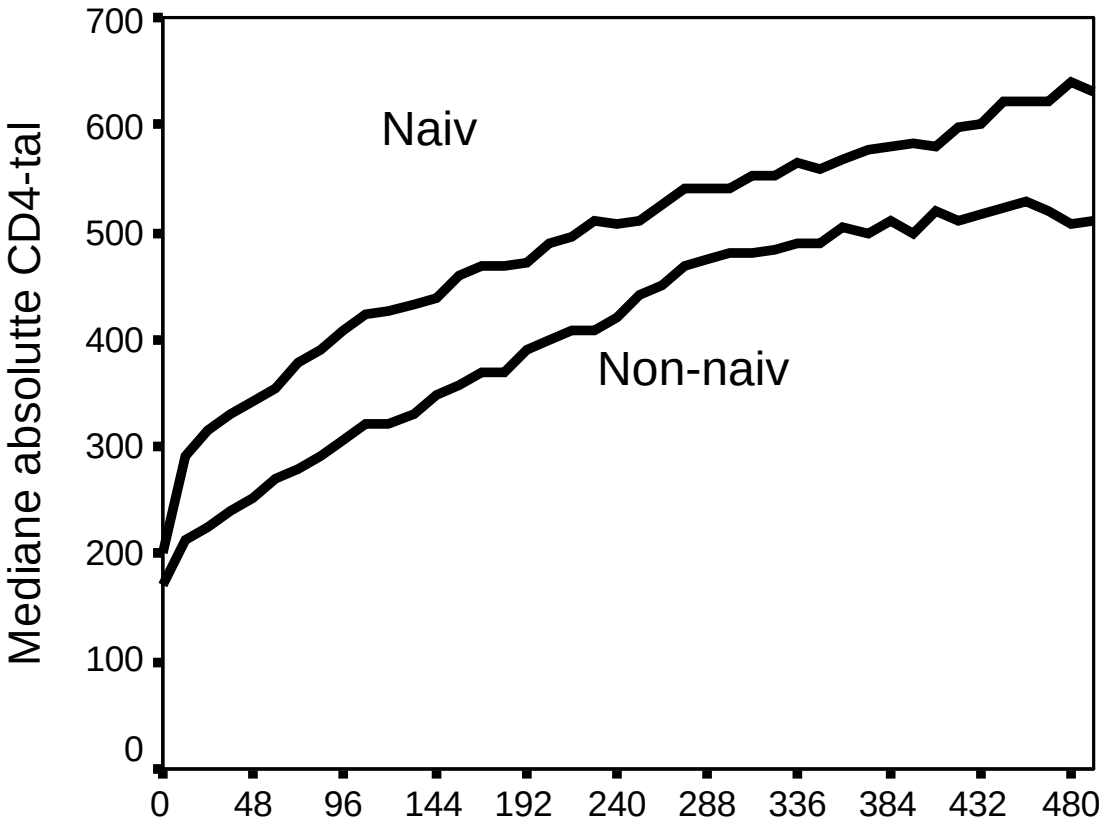
Viser mediane CD4 tal fordelt på uger efter start af HAART.



Fraktion med viral load < 500 fordelt på naive (ingen antiretroviral behandling før HAART) og non-naive (behandling med ét eller to stoffer før HAART).

Mediane CD4

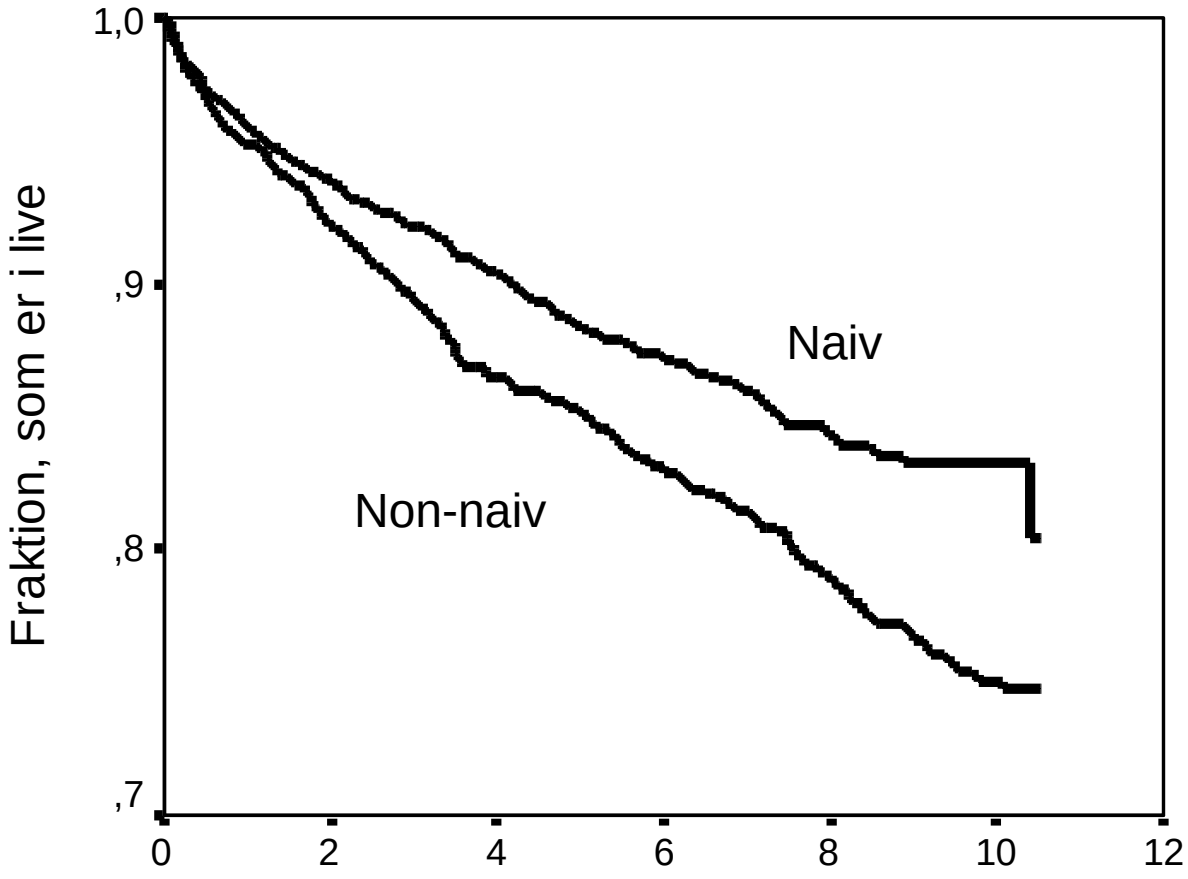
Fordelt på naiv og non-naiv



Viser mediane CD4 fordelt på behandlingsnaive og non-naive patienter.

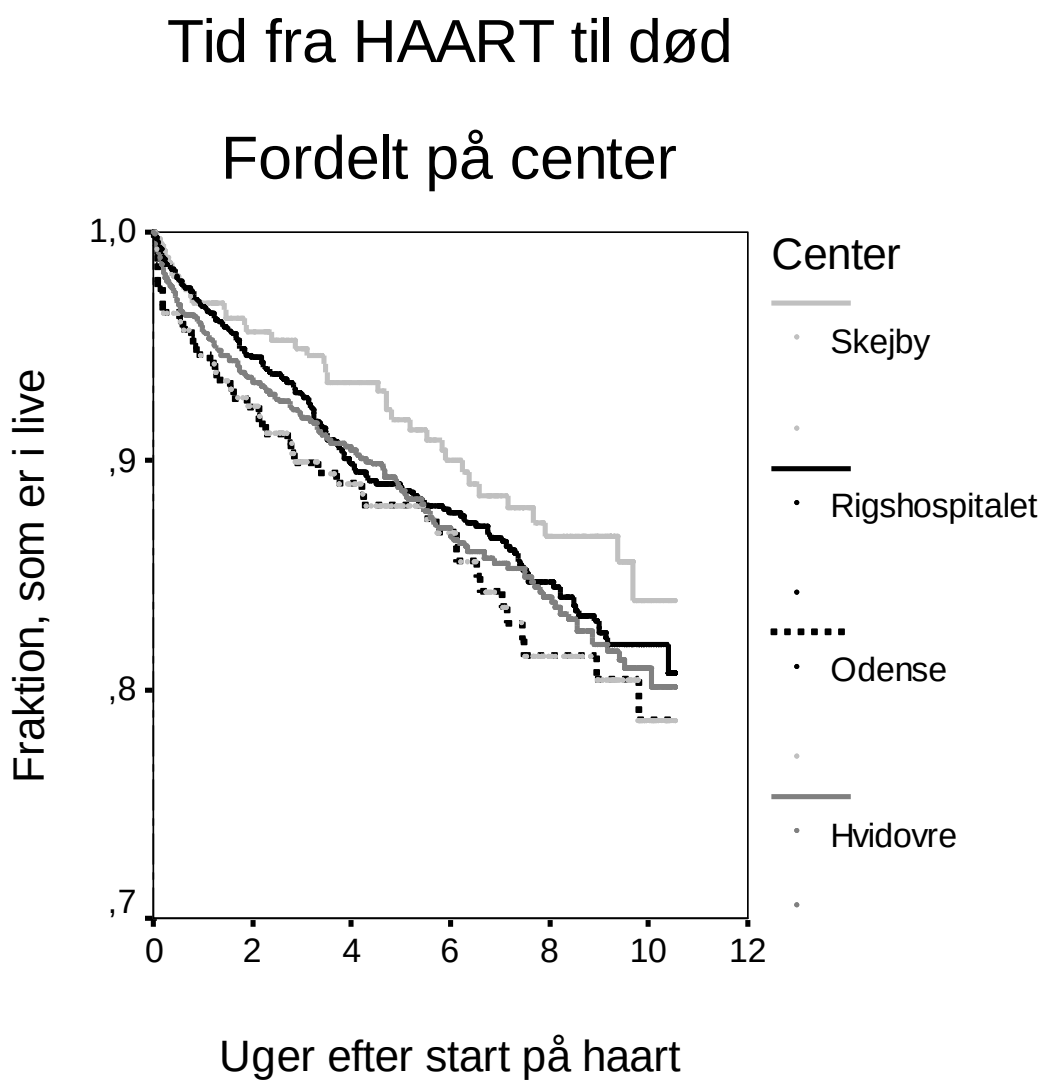
Tid fra HAART til død

Fordelt på naiv og non-naiv

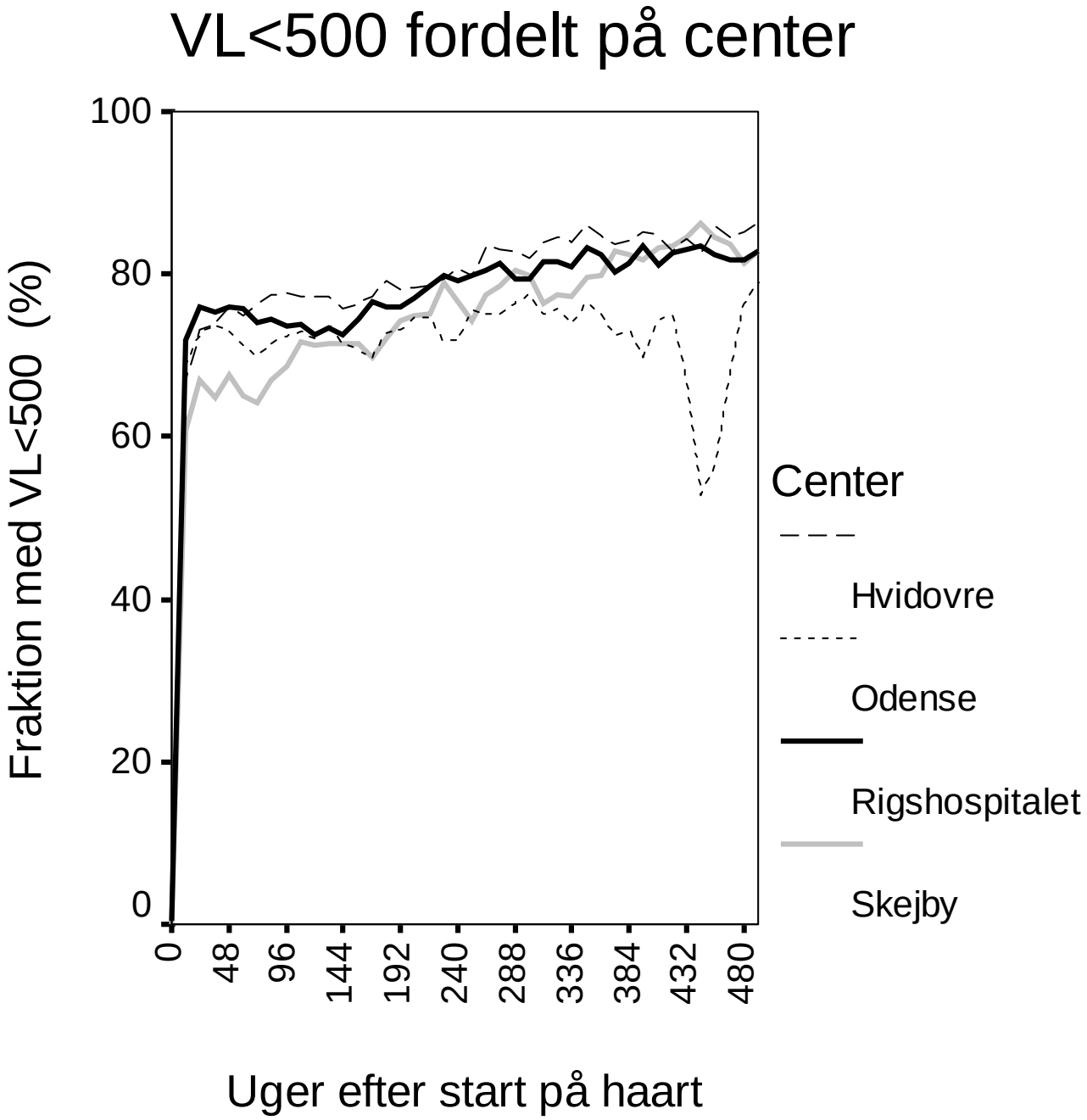


Kvalitetskontrol

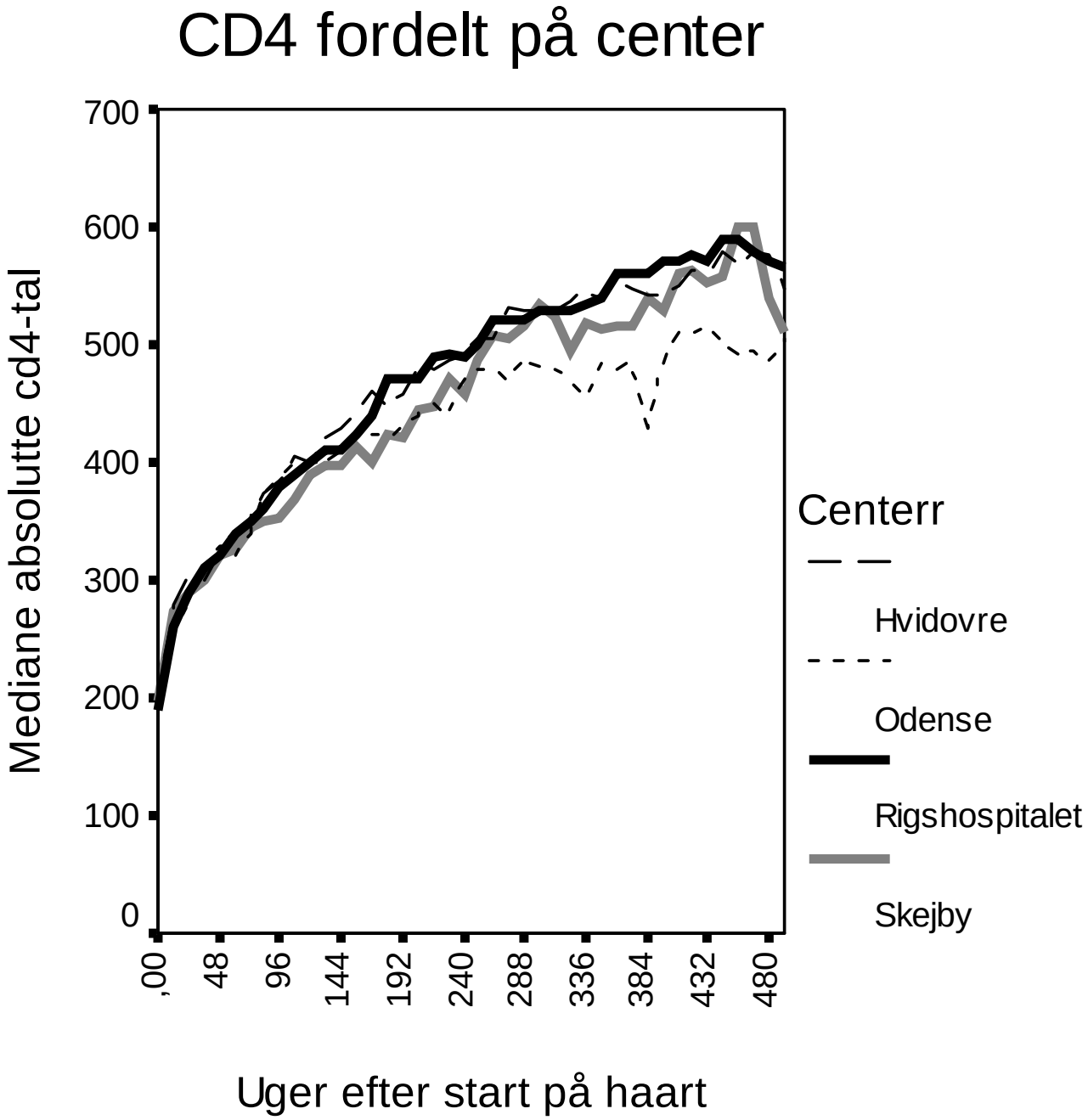
Den Danske HIV Kohorte kan også anvendes til kvalitetskontrol. Data fordelt på centre er offentliggjort med tilladelse fra professor, overlæge, dr. med. Jens Ole Nielsen, professor, overlæge, dr. med. Peter Skinhøj, professor, overlæge, dr. med. Court Pedersen og overlæge, dr. med. Lars Jørgen Østergaard, som er ansvarlige for de infektionsmedicinske afsnit i hhv. København (Hvidovre og Rigshospitalet), Odense og Århus (Skejby). Som det kan ses, er der ganske små forskelle på centrene, men disse er langt under, hvad der kan forventes ud fra tilfældig varians. De senere år har bl.a. STI (structured treatment interruptions) og studier som SMART medvirket til, at tidligere accepterede mål for behandlingssucces (undetectable viral load og CD4 tal) skal tolkes mere varsomt. Der er på ingen måde taget højde for den varians, der er mellem centrene i patientsammensætning. Der findes ikke i de center-relaterede data holdepunkter for reelle forskelle i behandlingsresultater, og de må ikke lede til overfortolkning af "de små tals magi".



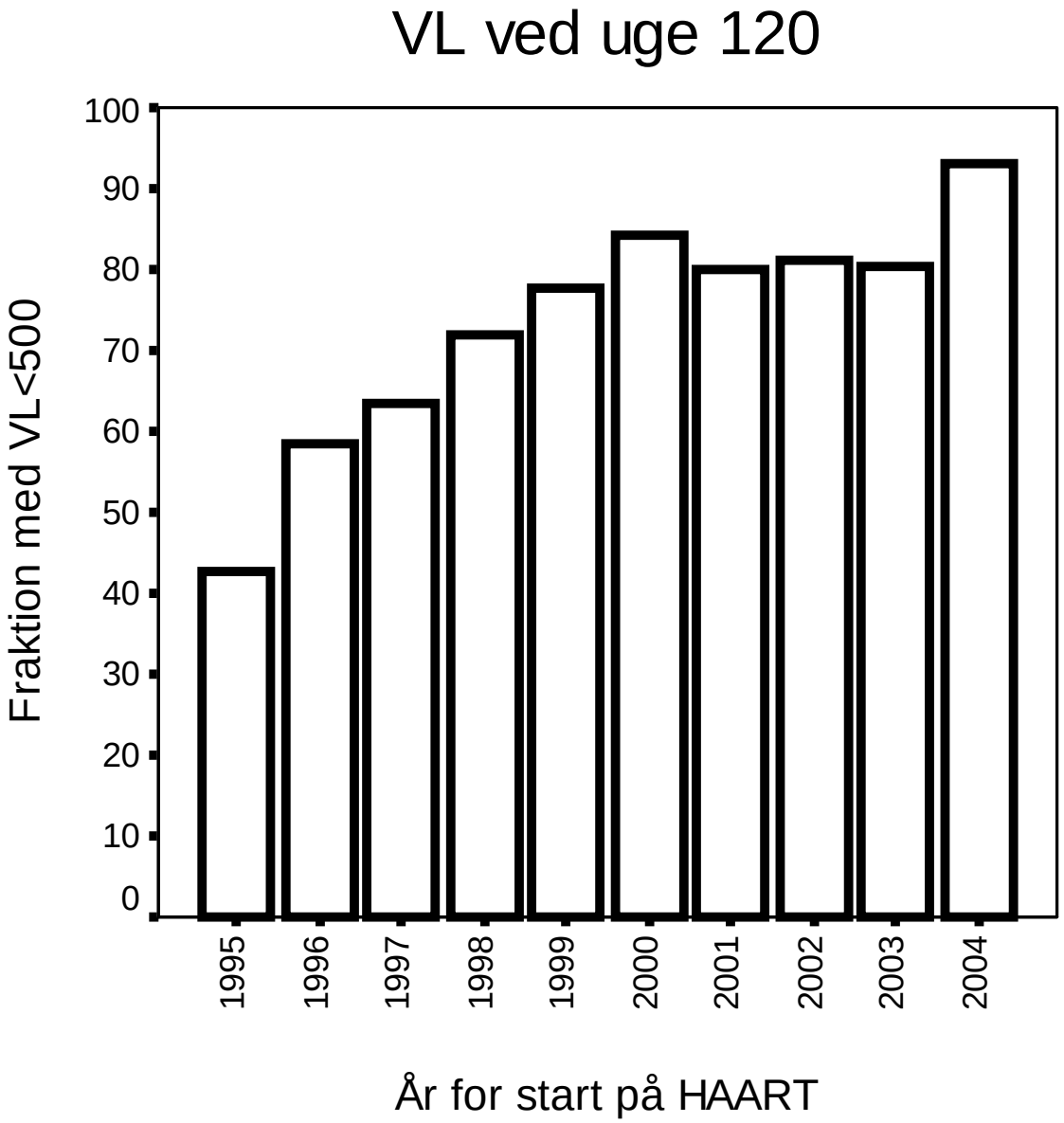
Viser Kaplan-Meier kurver for tid fra start af HAART til død for patienter ved de enkelte centre.



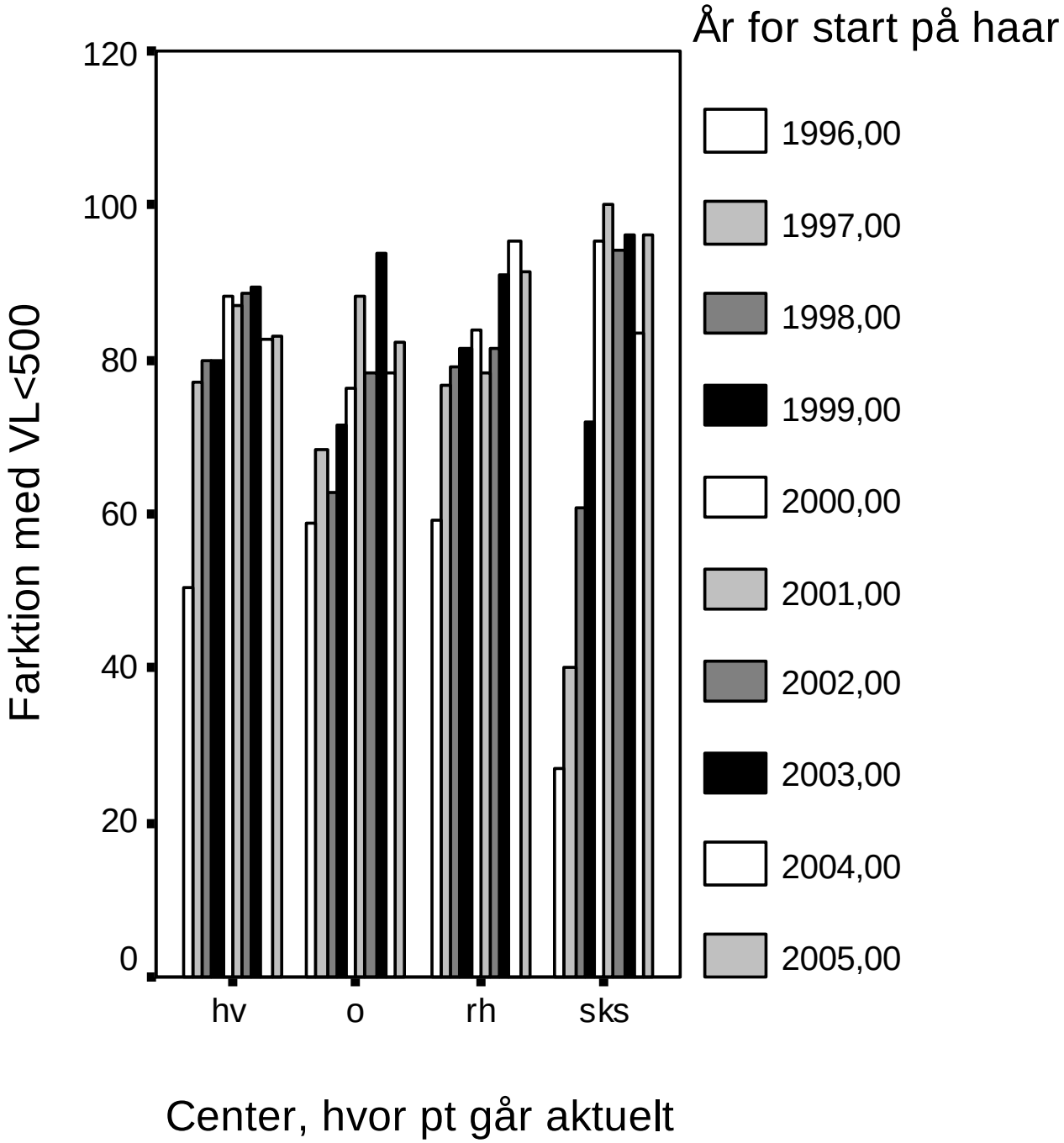
Viser fraktionen af patienter, som opnår et VL<500 fordelt på centre og uger efter start af HAART. Faldet for Odense Universitetshospital skyldes fejl i KMAs måling af VL, idet man en overgang målte for højt VL p. gr. a. en centrifugefejl.



Viser median for CD4-tal fordelt på centre og uger efter start af HAART.



Viser hvor stor en del af patienterne der opnår et VL<500 til uge 120 (og som har overlevet til uge 120), fordelt på, hvilket år de starter HAART. De patienter, som er opført i søjlen ”2002”, er således startet HAART i 2002, mens værdien for VL til uge 120 er bestemt 120 uger senere, altså i 2004. Det danner derfor heller ikke mening at medtage 2005 patienterne, da de først får målt deres 120 ugers værdi i 2007.



Viser fraktionen af patienter, som til uge 48 opnår et VL<500. De mørkegrå søjler angiver således de patienter, som startede HAART i 2003 og som fik målt et VL til uge 48 i 2004. Som det ses af figuren, er eventuelle tidligere forskelle mellem centrene i fraktionen af patienter, som opnår viral load < 500 udlignet over tid. Data for 2006 skal tolkes med varsomhed, idet der er mange patienter, som endnu ikke er kommet til uge 48 efter at være startet HAART i 2006.

De enkelte antiretrovirale præparater.

Den resterende del af rapporten omhandler data for anvendelse, skift og bivirkninger for de enkelte antiretrovirale præparater. Visse af tabellerne kan måske synes meget detaljerede, men flere af dem er fremkommet efter ønske fra medicinalindustrien. Såfremt en patient er ophørt med et præparat i mere end 3 måneder, betragtes det i de efterfølgende analyser, som endeligt seponeret. Derfor vil man se, at en patient undertiden kan genoptage behandlingen med det samme præparat. For de enkelte præparater er anvendt generiske navne, dog er der anvendt salgsnavne for kombinationspræparater.
For alle tabeller gælder, at et stof tælles med også såfremt det indgår i et kombinationspræparat. Det betyder, at en patient i behandling med trizivir tæller med i retrovir, epivir, abacavir og trizivir tabellerne.

Forklaring til tabellernes indhold:
I. Angiver antallet af patienter, som det år starter på præparatet første gang i et HAART regime. Det betyder, at såfremt en patient f.eks. er startet HAART i 1998 med stavudin og didanosin, men i 1999 starter på et regime med zidovudin og lamivudin, så tæller patienten med i 1998 for stavudin og didanosin, og i 1999 for zidovudin og lamivudin.

II. Angiver, hvor mange patienter, der det år er startet på et HAART regime for første gang og hvori præparatet indgår. I ovenstående eksempel ville patienten tælle med i 1998 for stavudin og didanosin, men ikke i 1999 for zidovudin og lamivudin.

III. Angiver, det totale antal patienter, der det år modtog behandling med præparatet som en del af et HAART regime. I ovenstående eksempel ville patienten for stavudin og didanosin tælle med i 1998 og 1999, og for zidovudin og lamivudin tælle med i 1999 og de følgende år frem til seponering.

IV. Angiver hvor mange patienter, der det år for første gang får seponeret præparatet. I ovenstående eksempel ville patienten tælle med for stavudin og didanosin i 1999.

V. Angiver, hvilke præparater, som patienten modtager, efter han har fået seponeret præparatet. En behandlingspause på under 3 måneder tælles ikke som en seponering. Derimod er en behandlingspause på mere en 3 måneder talt med som en seponering. Efterfølgende anvendelse af antivirale præparater er opdelt i NRTI og i NNRTI + PI. For NRTI er kun medtaget patienter, som skifter behandling efter 1. januar 2002, og for NNRTI og PI for perioden efter 1. januar 2003.

VI. Årsager til skift. For at vore data skal kunne bidrage til eventuelle større internationale kohortestudier, har vi initialt valgt at anvende den standard, som i 1990'erne blev anvendt i Eurosida. Denne standard er i dag delvist forældet. Dog vil man i tabellerne for mange præparaters vedkommende tydeligt kunne se, hvilke bivirkninger, der belaster præparates anvendelse og forårsager skift. Der er kun medtaget årsager til seponering efter 1. januar 2003.

Zidovudin

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Zidovudin (A16)

Årstal	Antal
1994	6
1995	34
1996	413
1997	604
1998	273
1999	241
2000	224
2001	314
2002	274
2003	221
2004	228
2005	143
2006	108

II. Antal patienter, som starter på HAART, hvori Zidovudin indgår (% af de patienter, som starter HAART det år) (G9)

Årstal	Antal
1994	6 (100%)
1995	34 (100%)
1996	409 (82,8%)
1997	588 (78,3%)
1998	251 (79,9%)
1999	210 (69,5%)
2000	190 (71,4%)
2001	256 (86,2%)
2002	215 (90,0%)
2003	193 (89,8%)
2004	201 (84,1%)
2005	134 (72,0%)
2006	99 (52,7%)

III. Antal patienter i behandling med Zidovudin (fordelt på år) (A1-15)

Årstal	Antal
1995	40
1996	451
1997	1008
1998	1066
1999	1153
2000	1225
2001	1456
2002	1655
2003	1791
2004	1878
2005	1824
2006	1360

IV. Første seponering af Zidovudin fordelt på årstal (A17)

Årstal	Antal
1995	1
1996	54
1997	228
1998	185
1999	193
2000	144
2001	119
2002	108
2003	116
2004	167
2005	460
2006	357

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Zidovudin (efter 1. januar 2002) (A18-25)

Præparat	Antal
Zidovudin*	129
Stavudin	54
Lamivudin	970
Didanosin	58
Zalcitabine	1
Abacavir	819
Tenofovir	253
Emtricitabin	158

***Såfremt, der er afholdt en pause på mere end 3 måneder anses Zidovudin for seponeret, hvorfor behandlingen senere kan initieres igen med Zidovudin.**

VI. Årsager til skift af Zidovudin skiftet efter 2003 (G13)

Årsager	Antal
Virologisk svigt (1)	82
Abnorm fedtfordeling (2)	138
Dyslipidæmi (3)	8
Overfølsomhed (4)	10
Gastrointestinale bivirkninger (5)	65
Neurologiske bivirkninger (6)	19
Toxicitet, overvejende nefrologisk (7)	0
Toxicitet, overvejende endokrinologisk (8)	4
Anden toxicitet (9)	172
Patientens ønske (10)	139
Lægens beslutning (11)	334
Anden årsag (12)	170
Ukendt (13)	11
Som led i skift til anden antiretroviral medicin(14)	250
Problemer med compliance (15)	116

Lamivudin

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Lamivudin

Årstal	Antal
1995	4
1996	456
1997	769
1998	317
1999	279
2000	235
2001	321
2002	257
2003	214
2004	237
2005	180
2006	138

II. Antal patienter, som starter på HAART, hvori Lamivudin indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	4 (11,8%)
1996	386 (78,0%)
1997	704 (93,7%)
1998	301 (95,9%)
1999	257 (85,1%)
2000	210 (78,9%)
2001	289 (97,3%)
2002	235 (98,3%)
2003	198 (92,1%)
2004	220 (92,1%)
2005	164 (88,2%)
2006	128 (68,1%)

III. Antal patienter i behandling med Lamivudin (fordelt på år)

Årstal	Antal
1995	4
1996	459
1997	1207
1998	1419
1999	1589
2000	1682
2001	1916
2002	2075
2003	2196
2004	2294
2005	2348
2006	2220

IV. Første seponering af Lamivudin fordelt på årstal

Årstal	Antal
1995	0
1996	22
1997	130
1998	163
1999	176
2000	144
2001	120
2002	108
2003	102
2004	104
2005	157
2006	198

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Lamivudin (efter 1. januar 2002).

Præparat	Antal
Zidovudin	181 (23,8%)
Stavudin	39 (5,1%)
Lamivudin	190 (25,0%)
Didanosin	65 (8,6%)
Zalcitabine	1 (0,1%)
Abacavir	154 (20,3%)
Tenofovir	356 (46,9%)
Emtricitabin	264 (34,8%)

VI. Årsager til skift af Lamivudin efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	128
Abnorm fedtfordeling (2)	22
Dyslipidæmi (3)	5
Overfølsomhed (4)	16
Gastrointestinale bivirkninger(5)	47
Neurologiske bivirkninger (6)	9
Nefrologiske bivirkninger (7)	2
Endokrinologiske bivirkninger (8)	4
Anden toxicitet (9)	73
Patientens ønske (10)	135
Lægens beslutning (11)	161
Anden årsag (12)	150
Ukendt (13)	9
Som led i skift til anden antiretroviral medicin(14)	113
Problemer med compliance (15)	134

Stavudin

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Stavudin

Årstal	Antal
1995	0
1996	102
1997	337
1998	174
1999	211
2000	164
2001	77
2002	48
2003	19
2004	13
2005	7
2006	1

II. Antal patienter, som starter på HAART, hvori Stavudin indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	0 (0,0%)
1996	71 (14,4%)
1997	156 (20,8%)
1998	59 (18,8%)
1999	75 (24,8%)
2000	65 (24,4%)
2001	14 (4,7%)
2002	10 (4,2%)
2003	3 (1,4%)
2004	6 (2,5%)
2005	4 (2,2%)
2006	1 (0,5%)

III. Antal patienter i behandling med Stavudin (fordelt på år)

Årstal	Antal
1995	0
1996	101
1997	431
1998	549
1999	675
2000	750
2001	712
2002	610
2003	436
2004	297
2005	178
2006	83

IV. Første seponering af Stavudin fordelt på årstal

Årstal	Antal
1995	0
1996	11
1997	70
1998	94
1999	103
2000	124
2001	148
2002	166
2003	127
2004	102
2005	71
2006	28

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Stavudin (efter 1. januar 2002).

Præparat	Antal
Zidovudin	160 (31,0%)
Stavudin	18 (3,5%)
Lamivudin	370 (71,7%)
Didanosin	77 (14,9%)
Zalcitabine	0 (0,0%)
Abacavir	293 (56,8%)
Tenofovir	109 (21,1%)
Emtricitabin	15 (2,9%)

VI. Årsager til skift af Stavudin efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	49
Abnorm fedtfordeling (2)	99
Dyslipidæmi (3)	16
Overfølsomhed (4)	2
Gastrointestinale bivirkninger(5)	12
Neurologiske bivirkninger (6)	30
Nefrologisk bivirkning (7)	1
Endokrinologiske bivirkninger (8)	3
Anden toxicitet (9)	14
Patientens ønske (10)	31
Lægens beslutning (11)	77
Anden årsag (12)	22
Ukendt (13)	8
Som led i skift til anden antiretroviral medicin(14)	21
Problemer med compliance (15)	23

Didanosin

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Didanosin

Årstal	Antal
1995	7
1996	126
1997	53
1998	57
1999	110
2000	141
2001	75
2002	51
2003	33
2004	34
2005	20
2006	7

II. Antal patienter, som starter på HAART, hvori Didanosin indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	7 (20,6%)
1996	119 (24,1%)
1997	30 (4,0%)
1998	6 (1,9%)
1999	49 (16,2%)
2000	56 (21,1%)
2001	12 (4,0%)
2002	4 (1,7%)
2003	2 (0,9%)
2004	1 (0,4%)
2005	0 (0,0%)
2006	0 (0,0%)

III. Antal patienter i behandling med Didanosin (fordelt på år)

Årstal	Antal
1995	7
1996	131
1997	120
1998	125
1999	212
2000	316
2001	336
2002	318
2003	293
2004	274
2005	251
2006	191

IV. Første seponering af Didanosin fordelt på årstal

Årstal	Antal
1995	2
1996	64
1997	67
1998	29
1999	49
2000	57
2001	71
2002	65
2003	49
2004	32
2005	55
2006	26

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Didanosin (efter 1. januar 2002).

Præparat	Antal
Zidovudin	96 (40,5%)
Stavudin	18 (7,6%)
Lamivudin	134 (56,5%)
Didanosin	19 (8,0%)
Zalcitabine	1 (0,4%)
Abacavir	116 (48,9%)
Tenofovir	80 (33,8%)
Emtricitabin	16 (6,8)

VI. Årsager til skift af Didanosin efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	33
Abnorm fedtfordeling (2)	18
Dyslipidæmi (3)	3
Overfølsomhed (4)	0
Gastrointestinale bivirkninger(5)	11
Neurologiske bivirkninger (6)	32
Toxicitet, overvejende nefrologisk (7)	1
Anden toxicitet (9)	24
Patientens ønske (10)	23
Lægens beslutning (11)	33
Anden årsag (12)	19
Ukendt (13)	2
Som led i skift til anden antiretroviral medicin(14)	6
Problemer med compliance (15)	32

Abacavir

I. Antal patienter fordelt på årstal, som første gang modtager behandling med Abacavir.

Årstal	Antal
1994	0
1995	0
1996	0
1997	9
1998	71
1999	177
2000	149
2001	245
2002	255
2003	155
2004	151
2005	433
2006	309

II. Antal patienter, som starter på HAART, hvori Abacavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	0 (0,0%)
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	8 (2,5%)
1999	43 (14,2%)
2000	34 (12,8%)
2001	67 (22,6%)
2002	36 (15,1%)
2003	16 (7,4%)
2004	10 (4,2%)
2005	21 (11,3%)
2006	28 (14,9%)

III. Antal patienter i behandling med Abacavir (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	9
1998	80
1999	229
2000	341
2001	527
2002	716
2003	795
2004	858
2005	1239
2006	1435

IV. Første seponering af Abacavir fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	0
1998	29
1999	45
2000	66
2001	89
2002	91
2003	99
2004	65
2005	87
2006	64

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Abacavir (efter 1. januar 2002).

Præparat	Antal
Zidovudin	191 (42,9%)
Stavudin	31 (7,0%)
Lamivudin	253 (56,9%)
Didanosin	60 (13,5%)
Zalcitabine	0 (0,0%)
Abacavir	75 (16,9%)
Tenofovir	121 (27,2%)
Emtricitabin	42 (9,4%)

VI. Årsager til skift af Abacavir efter 1 januar 2003.

Årsager	Antal
Virologisk svigt (1)	46
Abnorm fedtfordeling (2)	5
Dyslipidæmi (3)	0
Overfølsomhed (4)	47
Gastrointestinale bivirkninger(5)	51
Neurologiske bivirkninger (6)	10
Nefrologiske bivirkninger (7)	1
Endokrinologisk bivirkning (8)	1
Anden toxicitet (9)	56
Patientens ønske (10)	79
Lægens beslutning (11)	60
Anden årsag (12)	48
Ukendt (13)	2
Som led i skift til anden antiretroviral medicin(14)	17
Problemer med compliance (15)	76

Trizivir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Trizivir

Årstal	Antal
1994	0
1995	0
1996	0
1997	1
1998	19
1999	51
2000	54
2001	193
2002	185
2003	106
2004	30
2005	20
2006	11

II. Antal patienter, som starter på HAART, hvori Trizivir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	0 (0,0%)
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	7 (2,2%)
1999	7 (2,3%)
2000	9 (3,4%)
2001	43 (14,5%)
2002	23 (9,6%)
2003	14 (6,5%)
2004	1 (0,4%)
2005	2 (1,1%)
2006	0 (0,0%)

III. Antal patienter i behandling med Trizivir (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	1
1998	20
1999	70
2000	113
2001	295
2002	582
2003	625
2004	514
2005	406
2006	289

Tenofovir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med tenofovir

Årstal	Antal
1994	0
1995	0
1996	0
1997	0
1998	0
1999	1
2000	1
2001	1
2002	58
2003	141
2004	122
2005	171
2006	279

II. Antal patienter, som starter på HAART, hvori Tenofovir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	0 (0,0%)
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	0 (0,0%)
1999	0 (0,0%)
2000	1 (0,4%)
2001	0 (0,0%)
2002	1 (0,4%)
2003	5 (2,3%)
2004	8 (3,3%)
2005	15 (8,1%)
2006	60 (31,9%)

III. Antal patienter i behandling med Tenofovir (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	1
2000	1
2001	2
2002	60
2003	195
2004	289
2005	429
2006	653

IV. Første seponering af Tenofovir fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	1
2000	0
2001	0
2002	7
2003	32
2004	36
2005	53
2006	68

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Tenofovir (efter 1. januar 2002).

Præparat	Antal
Zidovudin	48 (23,4%)
Stavudin	9 (4,4%)
Lamivudin	101 (49,3%)
Didanosin	30 (14,6%)
Zalcitabine	0 (0,0%)
Abacavir	89 (43,4%)
Tenofovir	54 (26,3%)
Emtricitabin	54 (26,3%)

VI. Årsager til skift af Tenofovir efter 1 januar 2003.

Årsager	Antal
Virologisk svigt (1)	16
Abnorm fedtfordeling (2)	1
Dyslipidæmi (3)	1
Overfølsomhed (4)	2
Gastrointestinale bivirkninger(5)	25
Neurologiske bivirkninger (6)	3
Nefrologiske bivirkninger (7)	14
Endokrinologisk bivirkning (8)	0
Anden toxicitet (9)	32
Patientens ønske (10)	33
Lægens beslutning (11)	37
Anden årsag (12)	31
Ukendt (13)	5
Som led i skift til anden antiretroviral medicin(14)	6
Problemer med compliance (15)	32

Emtricitabin

I. Antal patienter fordelt på årstal, som første gang modtager behandling med Emtricitabin.

Årstal	Antal
1994	0
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	1
2002	1
2003	0
2004	1
2005	97
2006	307

II. Antal patienter, som starter på HAART, hvori Emtricitabin indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	0 (0,0%)
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	0 (0,0%)
1999	0 (0,0%)
2000	0 (0,0%)
2001	0 (0,0%)
2002	1 (0,4%)
2003	0 (0,0%)
2004	0 (0,0%)
2005	7 (3,8%)
2006	57 (30,3%)

III. Antal patienter i behandling med Emtricitabin (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	1
2002	2
2003	2
2004	3
2005	100
2006	405

IV. Første seponering af Emtricitabin fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	0
2002	0
2003	0
2004	0
2005	3
2006	37

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Emtricitabin (efter 1. januar 2002).

Præparat	Antal
Zidovudin	15
Stavudin	2
Lamivudin	35
Didanosin	3
Zalcitabine	0
Abacavir	18
Tenofovir	4
Emtricitabin	3

VI. Årsager til skift af Emtricitabin efter 1 januar 2003.

Årsager	Antal
Virologisk svigt (1)	0
Abnorm fedtfordeling (2)	0
Dyslipidæmi (3)	0
Overfølsomhed (4)	1
Gastrointestinale bivirkninger(5)	6
Neurologiske bivirkninger (6)	3
Nefrologiske bivirkninger (7)	1
Endokrinologisk bivirkning (8)	0
Anden toxicitet (9)	8
Patientens ønske (10)	13
Lægens beslutning (11)	9
Anden årsag (12)	6
Ukendt (13)	1
Som led i skift til anden antiretroviral medicin(14)	1
Problemer med compliance (15)	7

Nevirapin

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Nevirapin (A16)

Årstal	Antal
1994	0
1995	0
1996	3
1997	53
1998	133
1999	112
2000	97
2001	56
2002	40
2003	117
2004	124
2005	98
2006	42

II. Antal patienter, som starter på HAART, hvori Nevirapin indgår (% af de patienter, som starter HAART det år) (G9)

Årstal	Antal
1995	0 (0,0%)
1996	3 (0,6%)
1997	6 (0,8%)
1998	49 (15,6%)
1999	56 (18,5%)
2000	41 (15,4%)
2001	14 (4,7%)
2002	7 (2,9%)
2003	11 (5,1%)
2004	16 (6,7%)
2005	10 (5,4%)
2006	11 (5,9%)

III. Antal patienter i behandling med Nevirapin (fordelt på år) (A1-15)

Årstal	Antal
1995	0
1996	3
1997	55
1998	182
1999	248
2000	281
2001	270
2002	268
2003	341
2004	414
2005	434
2006	395

IV. Første seponering af Nevirapin fordelt på årstal (A17)

Årstal	Antal
1995	0
1996	0
1997	7
1998	44
1999	67
2000	65
2001	64
2002	47
2003	47
2004	67
2005	62
2006	32

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Nevirapin (efter 1. januar 2003) (C).

	Intet
Non boosted Saquinavir	1
Boosted Saquinavir	5
Non boosted Indinavir	0
Boosted Indinavir	0
Nelfinavir	8
Kaletra	69
Tipranavir	1
Amprenavir	2
Atazanavir	58
Efavirenz	39
Nevirapin	13

VI. Årsager til skift af Nevirapin efter 1. januar 2003 (G13)

Årsager	Antal
Virologisk svigt (1)	39
Abnorm fedtfordeling (2)	2
Dyslipidæmi (3)	2
Overfølsomhed (4)	21
Gastrointestinale bivirkninger(5)	25
Neurologiske bivirkninger (6)	5
Endokrinologiske bivirkninger (8)	3
Anden toxicitet (9)	33
Patientens ønske (10)	34
Lægens beslutning (11)	23
Anden årsag (12)	19
Ukendt (13)	7
Som led i skift til anden antiretroviral medicin(14)	16
Problemer med compliance (15)	22

Efavirenz

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Efavirenz

Årstal	Antal
1994	0
1995	0
1996	0
1997	1
1998	28
1999	198
2000	259
2001	404
2002	376
2003	335
2004	295
2005	215
2006	194

II. Antal patienter, som starter på HAART, hvori Efavirenz indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	0 (0,0%)
1996	0 (0,0%)
1997	1 (0,1%)
1998	2 (0,6%)
1999	22 (7,3%)
2000	61 (22,9%)
2001	190 (64,0%)
2002	187 (78,2%)
2003	169 (78,6%)
2004	177 (74,1%)
2005	130 (69,9%)
2006	129 (68,6%)

III. Antal patienter i behandling med Efavirenz (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	1
1998	29
1999	221
2000	447
2001	761
2002	1002
2003	1170
2004	1304
2005	1332
2006	1304

IV. Første seponering af Efavirenz fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	0
1998	6
1999	40
2000	93
2001	144
2002	159
2003	144
2004	167
2005	160
2006	101

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Efavirenz (efter 1. januar 2003).

	Intet
Non boosted Saquinavir	0
Boosted Saquinavir	20
Non boosted Indinavir	2
Boosted Indinavir	9
Nelfinavir	15
Kaletra	139
Tipranavir	1
Amprenavir	5
Atazanavir	125
Nevirapin	203
Efavirenz	47

VI. Årsager til skift af Efavirenz efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	75
Abnorm fedtfordeling (2)	3
Dyslipidæmi (3)	1
Overfølsomhed (4)	30
Gastrointestinale bivirkninger(5)	22
Neurologiske bivirkninger (6)	231
Endokrinologiske bivirkninger (8)	1
Anden toxicitet (9)	67
Patientens ønske (10)	79
Lægens beslutning (11)	62
Anden årsag (12)	91
Ukendt (13)	3
Som led i skift til anden antiretroviral medicin(14)	14
Problemer med compliance (15)	51

Non-boosted Saquinavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med non-boosted Saquinavir

Årstal	Antal
1994	5
1995	28
1996	51
1997	190
1998	32
1999	6
2000	3
2001	3
2002	7
2003	4
2004	2
2005	1
2006	1

II. Antal patienter, som starter på HAART, hvori non-boosted Saquinavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	5 (83,3%)
1995	28 (82,4%)
1996	49 (9,9%)
1997	159 (21,2%)
1998	16 (5,1%)
1999	0 (0,0%)
2000	1 (0,4%)
2001	0 (0,0%)
2002	1 (0,4%)
2003	0 (0,0%)
2004	0 (0,0%)
2005	0 (0,0%)
2006	0 (0,0%)

III. Antal patienter i behandling med non-boosted Saquinavir (fordelt på år)

Årstal	Antal
1995	33
1996	84
1997	251
1998	195
1999	116
2000	40
2001	31
2002	24
2003	20
2004	16
2005	14
2006	7

IV. Første seponering af non-boosted Saquinavir fordelt på årstal

Årstal	Antal
1995	0
1996	23
1997	95
1998	88
1999	70
2000	11
2001	9
2002	6
2003	6
2004	3
2005	7
2006	0

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af non-boosted Saquinavir (efter 1. januar 2003).

	Intet
Non boosted Saquinavir	0
Boosted Saquinavir	9
Non boosted Indinavir	0
Boosted Indinavir	0
Nelfinavir	0
Kaletra	3
Tipranavir	1
Amprenavir	4
Atazanavir	2
Nevirapin	1
Efavirenz	3

VI. Årsager til skift af Saquinavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	3
Abnorm fedtfordeling (2)	0
Dyslipidæmi (3)	0
Overfølsomhed (4)	0
Gastrointestinale bivirkninger(5)	0
Neurologiske bivirkninger (6)	0
Nefrologiske bivirkninger (7)	0
Endokrinologiske bivirkninger (8)	0
Anden toxicitet (9)	1
Patientens ønske (10)	1
Lægens beslutning (11)	0
Anden årsag (12)	8
Ukendt (13)	2
Som led i skift til anden antiretroviral medicin(14)	1
Problemer med compliance (15)	0

Boosted Saquinavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med boosted Saquinavir

Årstal	Antal
1994	1
1995	0
1996	37
1997	176
1998	144
1999	131
2000	135
2001	88
2002	55
2003	30
2004	12
2005	9
2006	3

II. Antal patienter, som starter på HAART, hvori boosted Saquinavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	1 (16,7%)
1995	0 (0,0%)
1996	28 (5,7%)
1997	78 (10,4%)
1998	58 (1856%)
1999	84 (27,8%)
2000	62 (23,3%)
2001	15 (5,1%)
2002	3 (1,3%)
2003	5 (2,3%)
2004	3 (1,3%)
2005	1 (0,5%)
2006	0 (0,0%)

III. Antal patienter i behandling med boosted Saquinavir (fordelt på år)

Årstal	Antal
1995	1
1996	38
1997	210
1998	299
1999	345
2000	391
2001	399
2002	374
2003	348
2004	288
2005	224
2006	179

IV. Første seponering af boosted Saquinavir fordelt på årstal

Årstal	Antal
1995	0
1996	4
1997	58
1998	86
1999	98
2000	80
2001	73
2002	66
2003	63
2004	66
2005	37
2006	36

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af boosted saquinavir (efter 1. januar 2003).

Præparat	Antal
Non boosted Saquinavir	2
Boosted Saquinavir	4
Non boosted Indinavir	0
Boosted Indinavir	2
Nelfinavir	2
Kaletra	39
Tipranavir	1
Amprenavir	2
Atazanavir	54
Nevirapin	66
Efavirenz	97

VI. Årsager til skift af boosted Saquinavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	18
Abnorm fedtfordeling (2)	6
Dyslipidæmi (3)	15
Overfølsomhed (4)	3
Gastrointestinale bivirkninger(5)	36
Neurologiske bivirkninger (6)	0
Nefrologiske bivirkninger (7)	1
Endokrinologiske bivirkninger (8)	1
Anden toxicitet (9)	9
Patientens ønske (10)	35
Lægens beslutning (11)	18
Anden årsag (12)	29
Ukendt (13)	10
Som led i skift til anden antiretroviral medicin(14)	20
Problemer med compliance (15)	5

Non-boosted Indinavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med non-boosted Indinavir

Årstal	Antal
1995	2
1996	307
1997	468
1998	124
1999	24
2000	15
2001	5
2002	7
2003	2
2004	1
2005	1
2006	0

II. Antal patienter, som starter på HAART, hvori non-boosted Indinavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	2 (5,9%)
1996	252 (51,0%)
1997	305 (40,6%)
1998	86 (27,4%)
1999	9 (3,0%)
2000	8 (3,0%)
2001	4 (1,3%)
2002	3 (1,3%)
2003	1 (0,5%)
2004	0 (0,0%)
2005	1 (0,7%)
2006	0 (0,0%)

III. Antal patienter i behandling med non-boosted Indinavir (fordelt på år)

Årstal	Antal
1995	2
1996	309
1997	748
1998	701
1999	572
2000	375
2001	226
2002	153
2003	101
2004	61
2005	42
2006	30

IV. Første seponering af non-boosted Indinavir fordelt på årstal

Årstal	Antal
1995	0
1996	32
1997	167
1998	165
1999	201
2000	145
2001	81
2002	42
2003	32
2004	17
2005	8
2006	7

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af non-boosted Indinavir (efter 1. januar 2003).

Præparat	Antal
Non boosted Saquinavir	0
Boosted Saquinavir	3
Non boosted Indinavir	0
Boosted Indinavir	9
Nelfinavir	0
Kaletra	11
Tipranavir	0
Amprenavir	1
Atazanavir	9
Nevirapin	8
Efavirenz	30

VI. Årsager til skift af non-boosted Indinavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	5
Abnorm fedtfordeling (2)	4
Dyslipidæmi (3)	4
Overfølsomhed (4)	0
Gastrointestinale bivirkninger(5)	0
Neurologiske bivirkninger (6)	0
Nefrologiske bivirkninger (7)	4
Endokrinologisk bivirkning (8)	1
Anden toxicitet (9)	2
Patientens ønske (10)	8
Lægens beslutning (11)	10
Anden årsag (12)	5
Ukendt (13)	12
Som led i skift til anden antiretroviral medicin(14)	4
Problemer med compliance (15)	4

Boosted Indinavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med boosted Indinavir

Årstal	Antal
1995	0
1996	4
1997	3
1998	18
1999	175
2000	200
2001	93
2002	33
2003	20
2004	8
2005	2
2006	0

II. Antal patienter, som starter på HAART, hvori boosted Indinavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	0 (2,8%)
1996	2 (0,4%)
1997	0 (0,0%)
1998	0 (0,0%)
1999	7 (2,3%)
2000	20 (7,5%)
2001	12 (4,0%)
2002	4 (1,7%)
2003	5 (2,3%)
2004	5 (2,1%)
2005	1 (0,5%)
2006	0 (0,0%)

III. Antal patienter i behandling med boosted Indinavir (fordelt på år)

Årstal	Antal
1995	0
1996	4
1997	6
1998	19
1999	188
2000	360
2001	371
2002	281
2003	215
2004	153
2005	85
2006	42

IV. Første seponering af boosted Indinavir fordelt på årstal

Årstal	Antal
1995	0
1996	1
1997	5
1998	8
1999	36
2000	87
2001	114
2002	90
2003	63
2004	71
2005	38
2006	15

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af boosted Indinavir (efter 1. januar 2003).

Præparat	Antal
Non boosted Saquinavir	0
Boosted Saquinavir	5
Non boosted Indinavir	2
Boosted Indinavir	5
Nelfinavir	1
Kaletra	32
Tipranavir	1
Amprenavir	2
Atazanavir	47
Nevirapin	22
Efavirenz	89

VI. Årsager til skift af boosted Indinavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	10
Abnorm fedtfordeling (2)	15
Dyslipidæmi (3)	22
Overfølsomhed (4)	1
Gastrointestinale bivirkninger(5)	10
Neurologiske bivirkninger (6)	2
Nefrologiske bivirkninger (7)	20
Endokrinologiske bivirkninger (8)	3
Anden toxicitet (9)	18
Patientens ønske (10)	14
Lægens beslutning (11)	18
Anden årsag (12)	21
Ukendt (13)	9
Som led i skift til anden antiretroviral medicin(14)	9
Problemer med compliance (15)	14

Nelfinavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Nelfinavir

Årstal	Antal
1994	0
1995	0
1996	4
1997	65
1998	312
1999	313
2000	110
2001	32
2002	15
2003	8
2004	5
2005	1
2006	0

II. Antal patienter, som starter på HAART, hvori Nelfinavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	0 (0,0%)
1996	4 (0,8%)
1997	7 (0,9%)
1998	94 (29,9%)
1999	125 (41,4%)
2000	76 (28,6%)
2001	21 (7,1%)
2002	8 (3,3%)
2003	3 (1,4%)
2004	1 (0,4%)
2005	0 (0,0%)
2006	0 (0,0%)

III. Antal patienter i behandling med Nelfinavir (fordelt på år)

Årstal	Antal
1995	0
1996	4
1997	68
1998	375
1999	634
2000	591
2001	460
2002	327
2003	232
2004	170
2005	119
2006	74

IV. Første seponering af Nelfinavir fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	6
1998	64
1999	152
2000	160
2001	133
2002	101
2003	61
2004	46
2005	35
2006	18

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Nelfinavir (efter 1. januar 2003).

Præparat	Antal
Non boosted Saquinavir	0
Boosted Saquinavir	4
Non boosted Indinavir	0
Boosted Indinavir	0
Nelfinavir	5
Kaletra	42
Tipranavir	1
Amprenavir	1
Atazanavir	24
Nevirapin	33
Efavirenz	68

VI. Årsager til skift af Nelfinavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	59
Abnorm fedtfordeling (2)	8
Dyslipidæmi (3)	6
Overfølsomhed (4)	0
Gastrointestinale bivirkninger(5)	33
Neurologiske bivirkninger (6)	5
Nefrologiske bivirkninger (7)	0
Endokrinologiske bivirkninger (8)	0
Anden toxicitet (9)	3
Patientens ønske (10)	34
Lægens beslutning (11)	49
Anden årsag (12)	23
Ukendt (13)	11
Som led i skift til anden antiretroviral medicin(14)	21
Problemer med compliance (15)	11

Kaletra (Boosted Lopinavir)

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Kaletra

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	8
2000	75
2001	162
2002	82
2003	136
2004	183
2005	108
2006	96

II. Antal patienter, som starter på HAART, hvori Kaletra indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	0 (0,0%)
1999	7 (2,3%)
2000	4 (1,5%)
2001	12 (4,0%)
2002	4 (1,7%)
2003	23 (10,7%)
2004	47 (19,7%)
2005	44 (23,7%)
2006	30 (16,0%)

III. Antal patienter i behandling med Kaletra (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	8
2000	83
2001	237
2002	288
2003	388
2004	509
2005	501
2006	472

IV. Første seponering af Kaletra fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	0
2000	7
2001	35
2002	49
2003	64
2004	111
2005	115
2006	63

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Kaletra (efter 1. januar 2003).

Præparat	Antal
Non boosted Saquinavir	1
Boosted Saquinavir	17
Non boosted Indinavir	4
Boosted Indinavir	5
Nelfinavir	9
Kaletra	25
Tipranavir	9
Amprenavir	11
Atazanavir	131
Nevirapin	32
Efavirenz	103

VI. Årsager til skift af Kaletra efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	24
Abnorm fedtfordeling (2)	1
Dyslipidæmi (3)	13
Overfølsomhed (4)	1
Gastrointestinale bivirkninger(5)	111
Neurologiske bivirkninger (6)	4
Nefrologiske bivirkninger (7)	0
Endokrinologiske bivirkninger (8)	3
Anden toxicitet (9)	23
Patientens ønske (10)	45
Lægens beslutning (11)	30
Anden årsag (12)	51
Ukendt (13)	12
Som led i skift til anden antiretroviral medicin(14)	14
Problemer med compliance (15)	29

Amprenavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Amprenavir

Årstal	Antal
1995	0
1996	0
1997	0
1998	2
1999	3
2000	5
2001	20
2002	5
2003	20
2004	5
2005	6
2006	2

II. Antal patienter, som starter på HAART, hvori Amprenavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	0 (0,0%)
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	0 (0,0%)
1999	2 (0,6%)
2000	2 (0,7%)
2001	0 (0,0%)
2002	0 (0,0%)
2003	0 (0,0%)
2004	0 (0,0%)
2005	0 (0,0%)
2006	0 (0,0%)

III. Antal patienter i behandling med Amprenavir (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	0
1998	2
1999	3
2000	6
2001	24
2002	24
2003	40
2004	36
2005	34
2006	26

IV. Første seponering af Amprenavir fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	0
1998	2
1999	2
2000	2
2001	5
2002	7
2003	7
2004	7
2005	7
2006	5

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Amprenavir (efter 1. januar 2003).

Præparat	Antal
Non boosted Saquinavir	0
Boosted Saquinavir	4
Non boosted Indinavir	0
Boosted Indinavir	0
Nelfinavir	0
Kaletra	5
Tipranavir	2
Amprenavir	4
Atazanavir	6
Nevirapin	1
Efavirenz	1

VI. Årsager til skift af Amprenavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	6
Abnorm fedtfordeling (2)	0
Dyslipidæmi (3)	0
Overfølsomhed (4)	1
Gastrointestinale bivirkninger(5)	2
Neurologiske bivirkninger (6)	0
Nefrologiske bivirkninger (7)	0
Endokrinologiske bivirkninger (8)	0
Anden toxicitet (9)	1
Patientens ønske (10)	2
Lægens beslutning (11)	2
Anden årsag (12)	5
Ukendt (13)	2
Som led i skift til anden antiretroviral medicin(14)	0
Problemer med compliance (15)	4

Tipranavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Tipranavir

Årstal	Antal
1994	0
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	3
2002	0
2003	13
2004	5
2005	7
2006	2

II. Antal patienter, som starter på HAART, hvori Tipranavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	0 (0,0%)
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	0 (0,0%)
1999	0 (0,0%)
2000	0 (0,0%)
2001	0 (0,0%)
2002	0 (0,0%)
2003	0 (0,0%)
2004	0 (0,0%)
2005	0 (0,0%)
2006	0 (0,0%)

III. Antal patienter i behandling med Tipranavir (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	3
2002	1
2003	14
2004	18
2005	20
2006	19

IV. Første seponering af Tipranavir fordelt på årstal

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	2
2002	0
2003	1
2004	5
2005	2
2006	9

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Tipranavir (efter 1. januar 2003).

	Intet
Non boosted Saquinavir	0
Boosted Saquinavir	0
Non boosted Indinavir	0
Boosted Indinavir	0
Nelfinavir	0
Kaletra	5
Tipranavir	1
Amprenavir	1
Atazanavir	1
Nevirapin	1
Efavirenz	6

VI. Årsager til skift af Tipranavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	6
Abnorm fedtfordeling (2)	0
Dyslipidæmi (3)	0
Overfølsomhed (4)	0
Gastrointestinale bivirkninger(5)	2
Neurologiske bivirkninger (6)	0
Nefrologiske bivirkninger (7)	0
Endokrinologiske bivirkninger (8)	0
Anden toxicitet (9)	0
Patientens ønske (10)	1
Lægens beslutning (11)	2
Anden årsag (12)	4
Ukendt (13)	0
Som led i skift til anden antiretroviral medicin(14)	3
Problemer med compliance (15)	0

Atazanavir

I. Antal patienter fordelt på årstal, som for første gang modtager behandling med Atazanavir

Årstal	Antal
1994	0
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	0
2002	0
2003	6
2004	157
2005	260
2006	179

II. Antal patienter, som starter på HAART, hvori Atazanavir indgår (% af de patienter, som starter HAART det år)

Årstal	Antal
1994	0 (0,0%)
1995	0 (0,0%)
1996	0 (0,0%)
1997	0 (0,0%)
1998	0 (0,0%)
1999	0 (0,0%)
2000	0 (0,0%)
2001	0 (0,0%)
2002	0 (0,0%)
2003	0 (0,0%)
2004	6 (2,5%)
2005	13 (7,0%)
2006	14 (7,4%)

III. Antal patienter i behandling med Atazanavir (fordelt på år)

Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	0
2002	0
2003	6
2004	162
2005	402
2006	522

IV. Første seponering af Atazanavir fordelt på årstal

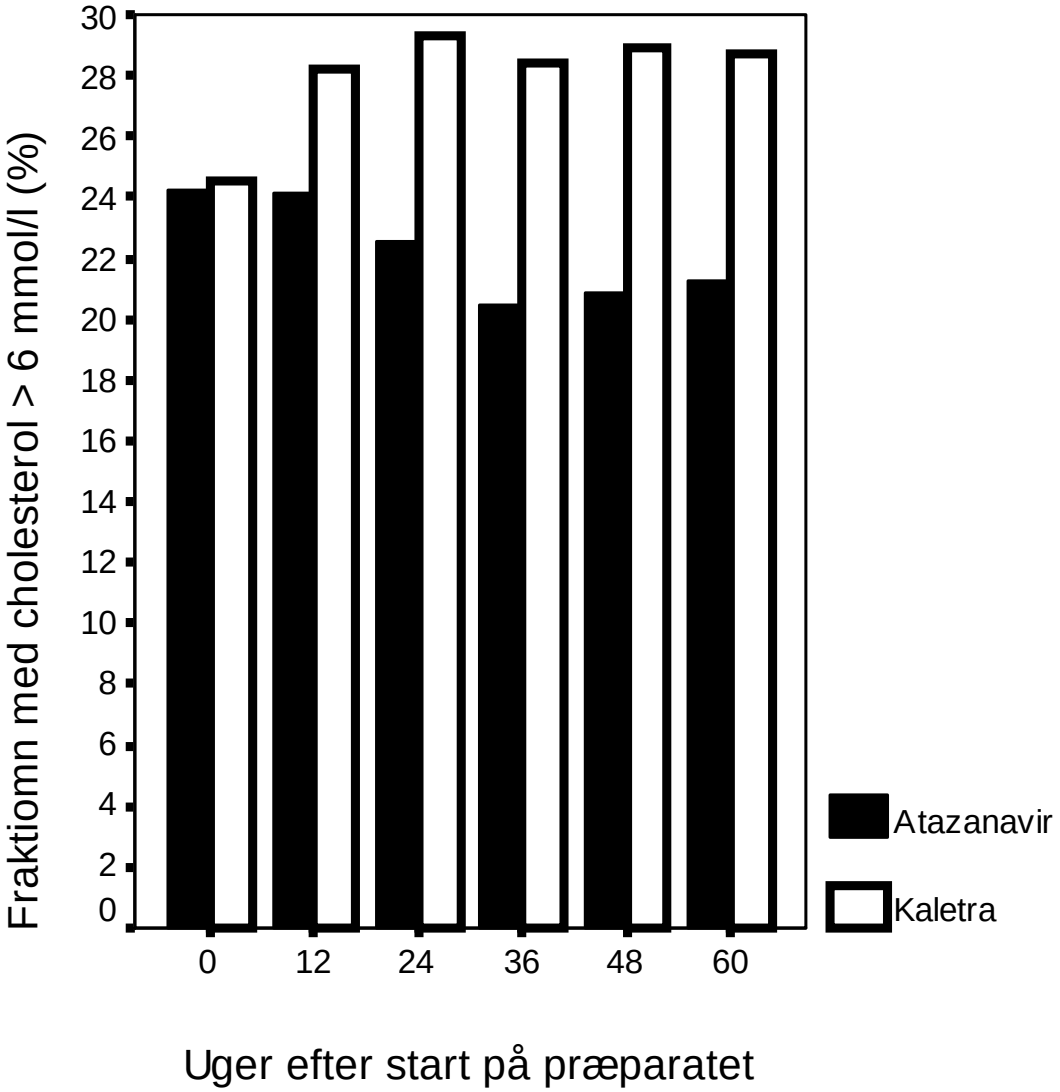
Årstal	Antal
1995	0
1996	0
1997	0
1998	0
1999	0
2000	0
2001	0
2002	0
2003	0
2004	25
2005	55
2006	55

V. Antiretrovirale præparater, som indgår i det første regime anvendt umiddelbart efter seponering af Atazanavir (efter 1. januar 2003).

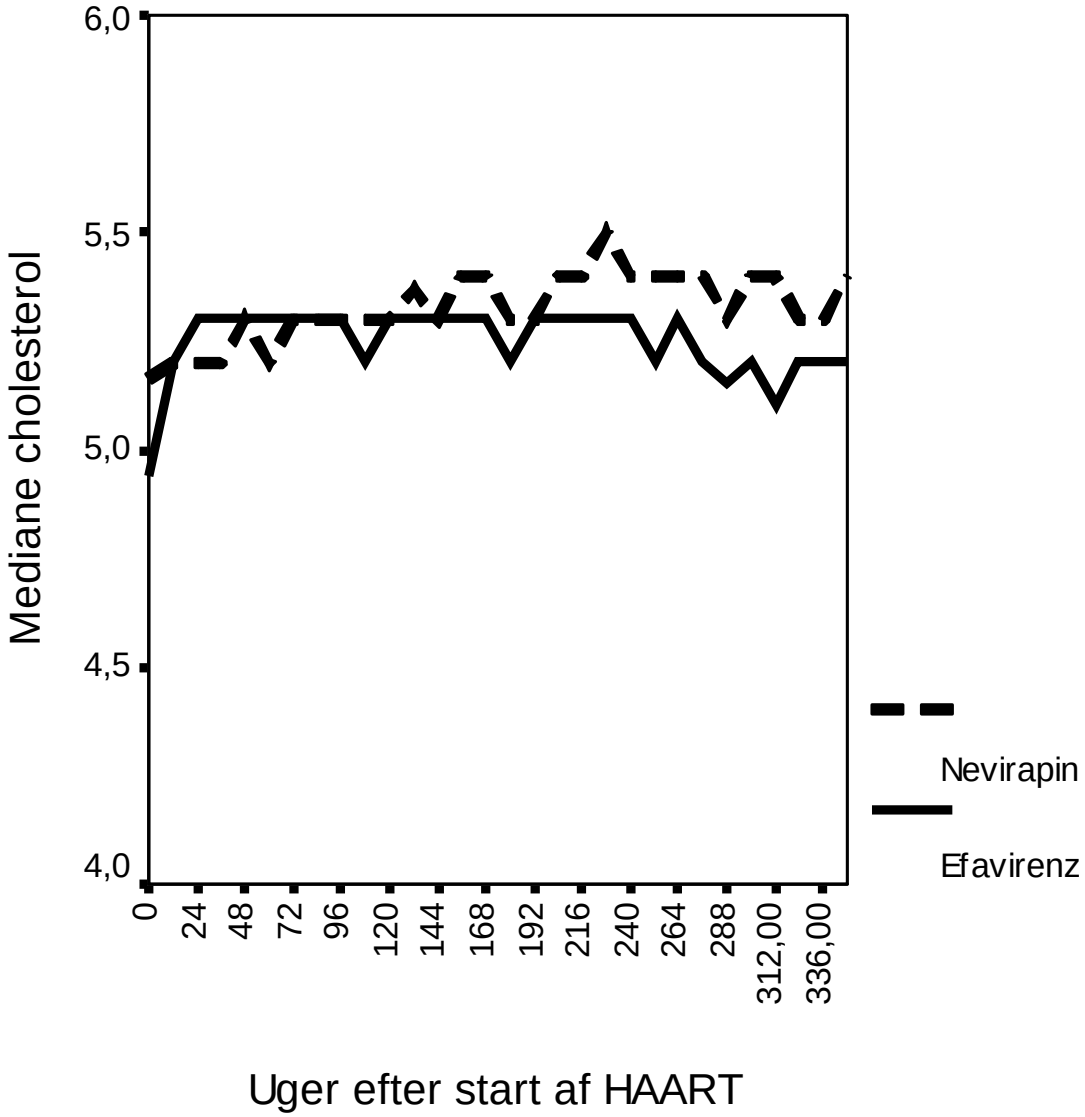
Præparat	Antal
Non boosted Saquinavir	2
Boosted Saquinavir	4
Non boosted Indinavir	0
Boosted Indinavir	4
Nelfinavir	5
Kaletra	37
Tipranavir	0
Amprenavir	2
Atazanavir	16
Nevirapin	17
Efavirenz	26

VI. Årsager til skift af Atazanavir efter 1. januar 2003

Årsager	Antal
Virologisk svigt (1)	1
Abnorm fedtfordeling (2)	3
Dyslipidæmi (3)	2
Overfølsomhed (4)	5
Gastrointestinale bivirkninger(5)	21
Neurologiske bivirkninger (6)	1
Nefrologiske bivirkninger (7)	0
Endokrinologiske bivirkninger (8)	4
Anden toxicitet (9)	19
Patientens ønske (10)	16
Lægens beslutning (11)	14
Anden årsag (12)	16
Ukendt (13)	9
Som led i skift til anden antiretroviral medicin(14)	5
Problemer med compliance (15)	26



Figuren viser den fraktion af patienter, som har et kolesterol over 6, fordelt på uger efter start af Atazanavir eller Kaletra. Man skal være opmærksom på, at der på ingen måde i analysen er taget højde for, at der sandsynligvis er store forskelle i de grupper, der starter de to præparater. Bl. a. er der ikke taget højde for, at der kan være forskelle i køn, alder, forudgående antiretroviral behandling og anden medicinsk benhandling.



Figuren viser kolesterolniveau hos patienter, som er startet nevirapin og efavirenz fordelt på uger efter start. Data er ikke korrigeret for forskelle i de to patientgruppers eventuelle forskelle i baseline karakteristika.

Annals of Internal Medicine | ARTICLE

Survival of Persons with and without HIV Infection in Denmark, 1995–2005

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Background: The expected survival of HIV-infected patients is of major public health interest.

Objective: To estimate survival time and age-specific mortality rates of an HIV-infected population compared with that of the general population.

Design: Population-based cohort study.

Setting: All HIV-infected persons receiving care in Denmark from 1995 to 2005.

Patients: Each member of the nationwide Danish HIV Cohort Study was matched with as many as 99 persons from the general population according to sex, date of birth, and municipality of residence.

Measurements: The authors computed Kaplan–Meier life tables with age as the time scale to estimate survival from age 25 years. Patients with HIV infection and corresponding persons from the general population were observed from the date of the patient's HIV diagnosis until death, emigration, or 1 May 2005.

Results: 3990 HIV-infected patients and 379 872 persons from the general population were included in the study, yielding 22 744 (median, 5.8 y/person) and 2 689 287 (median, 8.4 years/person) person-years of observation. Three percent of participants were lost to follow-up. From age 25 years, the median survival was 19.9 years (95% CI, 18.5 to 21.3) among patients with HIV infection and 51.1 years (CI, 50.9 to 51.5) among the general population. For HIV-infected patients, survival increased to 32.5 years (CI, 29.4 to 34.7) during the 2000 to 2005 period. In the subgroup that excluded persons with known hepatitis C coinfection (16%), median survival was 38.9 years (CI, 35.4 to 40.1) during this same period. The relative mortality rates for patients with HIV infection compared with those for the general population decreased with increasing age, whereas the excess mortality rate increased with increasing age.

Limitations: The observed mortality rates are assumed to apply beyond the current maximum observation time of 10 years.

Conclusions: The estimated median survival is more than 35 years for a young person diagnosed with HIV infection in the late highly active antiretroviral therapy era. However, an ongoing effort is still needed to further reduce mortality rates for these persons compared with the general population.

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Knowing the expected survival of HIV-infected patients is of major public health interest. Mortality rates have decreased substantially in recent years as a result of improved effectiveness of highly active antiretroviral therapy (HAART) (1). Studies comparing mortality rates for HIV-infected persons with age- and sex-specific mortality rates for the general population (2–5) have reported 3- to 10-fold increase in successfully treated patients. The relative mortality rate, however, is highly dependent on the age distribution of the study sample and does not in itself answer questions about survival. We therefore aimed to estimate median survival and age-specific mortality rates for an entire HIV-infected population compared with a cohort from the general population. Persons with HIV infection were followed from before initiation of HAART and included those with such predictors of lower survival as poor response to therapy, AIDS diagnosis, low CD4 count, high viral load, and poor adherence to treatment (6, 7). Linking data from the population-based Danish HIV Cohort Study (DHCS) (8) and the Danish Civil Registration System (CRS) (9, 10) allowed us to use product-limit methods that are analogous to the period life tables used by national authorities for estimating median survival (11).

METHODS

Study Sample

The DHCS is a prospective, nationwide, population-based cohort study of all HIV-infected persons treated in Danish HIV clinics since 1 January 1995 (8, 12). The study is ongoing, with continuous enrollment of both newly diagnosed residents and immigrants with existing HIV infection. Treatment for HIV infection in Denmark is restricted to 8 specialized centers, and the Danish health care system provides free tax-supported medical care, including antiretroviral treatment for HIV infection. The study databases are updated annually. Adult (>16 years) DHCS participants with residency in Denmark were included at their first visit to an HIV clinic. The Civil Registration System (CRS) is a national registry of all Danish

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Context

The expected survival of HIV-infected patients has been difficult to measure by comparing selected HIV samples and control groups.

Contribution

Denmark carefully tracks each of its residents' vital status, which makes it possible to accurately compare survival of HIV-infected persons and uninfected persons. In 2000 to 2005, life expectancy at age 25 years was 51 years in the general population and 39 years for HIV-infected persons without hepatitis C virus infection (HCV).

Cautions

Denmark provides excellent access to HIV and HCV care, so the results may be atypical.

Implications

Persons with HIV infection have a good, but far from normal, life expectancy.

—The Editors

residents; this registry contains information on date of birth; sex; address; date of migration; and date of death, if applicable (9). A 10-digit personal number (Central Person Registry [CPR] number), assigned at birth, uniquely identifies each person. The CRS is updated within a week of a person's birth, address change, death, or emigration. Use of the CPR number enables treatment centers to avoid multiple registrations of the same patient and allows tracking of deaths and persons lost to follow-up due to emigration. Using the CRS records, we drew a random sample of persons from the general population and matched them to each HIV-infected patient according to sex and month of birth and residence in the same municipality as the patient on the date of diagnosis (Denmark has a population of approximately 5.3 million persons living in 270 municipalities). We aimed to sample 99 persons from the general population for each HIV-infected person. However, because of a shortage of eligible persons in some municipalities, the mean number of persons from the general population per patient was 95.2 in the final sample.

Patients with at least 1 positive result on a hepatitis C virus (HCV)–antibody test or a positive result on an HCV RNA test were considered to be HCV-positive; the other patients were considered to be HCV-negative. The HCV-antibody status was available for 88.4% of all patients and for 95.4% of patients observed during 2000 to 2005. We did not have individual data on HCV infection in the general population, but the estimated prevalence in Denmark is only 3 per 1000 (13). Highly active antiretroviral therapy was defined as the combination of antiretroviral treatment with at least 3 drugs, including at least 1 protease inhibitor, 1 nonnucleoside reverse transcriptase inhibitor, or abacavir; or the 2-drug combination of efavirenz- and ritonavir-boosted lopinavir. Treatment interruption was defined as a period of at least 2 weeks after initiation of HAART during which the patient did not take antiretroviral drugs. Structured treatment interruptions have generally not been recommended in Denmark. Causes of death extracted from patient files were available for patients in DHCS and were divided into HIV-related causes (AIDS-defining illnesses and bacterial infections, corresponding to International Classification of Disease, Tenth Revision [ICD-10], codes A02, A07.2-07.3, A15-19, A31, A81.2, B00, B20-25, B37-39, B45, B58, C46, C53, C83.4, C83.9, F02.4, and J13-17), non–HIV-related other causes, and unknown causes.

Statistical Analysis

We computed Kaplan–Meier life tables using age as the time scale. Persons with HIV infection were observed from the date of HIV diagnosis or from the first visit to an HIV clinic, if the visit occurred at a later date; persons from the general population were observed starting at the same time as their matched HIV-infected patients. All persons were censored at emigration or on 1 May 2005. Death from any cause was the outcome event.

We estimated median survival times and computed mortality rates from age 25 years separately for men and women and for the subgroup of HCV-negative persons. We chose 25 years because this was the youngest age group with a sufficient number of patients ($n = 170$) being observed. We performed analyses for 3 clinically relevant periods: 1995 to 1996 (pre-HAART), 1997 to 1999 (early HAART), and 2000 to 2005 (late HAART) and with respect to the length of HAART treatment: before HAART, first year, second and third years, fourth and fifth years, and sixth year onward.

We computed mortality rates in 5-year age intervals and estimated crude relative (mortality rate ratio [mortality rate for patients with HIV infection divided by the mortality rate for the general population]) and absolute (excess mortality rate [mortality rate for the general population subtracted from the mortality rate for patients with HIV infection]) effects in HIV-infected patients compared with persons from the general population. In accordance with the matched design, we used a stratified Cox regression model for the mortality rate ratio estimations. When comparing mortality rate ratios from the stratified model with crude mortality rate ratios, we found only small deviations (median, 4.3% [interquartile range, 1.2% to 7.0%]) and therefore used standard statistical methods for the excess mortality rates. We further examined mortality rate ratios and excess mortality rates for the late HAART period and for HCV-negative and HCV-positive persons during the late HAART period.

Data analysis was performed by using Stata statistical software, version 9.0 (Stata Corp., College Station, Texas).

Table 1. **Characteristics of Study Participants***

Variable	Patients with HIV Infection	General Population without HIV Infection
Persons, *n*	3990	379 872
Men, %	77	77
Median age at study entry (interquartile range), *y*	37.2 (31.0–44.8)	36.9 (30.9–44.6)
Median observation time (interquartile range), *y*	5.8 (2.2–9.9)	8.4 (4.3–10.3)
Incident cases (diagnosed after 1 January 1995), *n (%)*	2045 (51)	–
Entered the cohort within 31 days after diagnosis	1556 (76)	–
Entered the cohort within 181 days after diagnosis	1943 (95)	–
Most likely method of infection, *n (%)*		
Male homosexual activity	1863 (47)	–
Heterosexual activity	1377 (35)	–
Intravenous drug use	480 (12)	–
Other	270 (7)	–
Race, *n (%)*		
Caucasian	3287 (82)	NA
Black	446 (11)	NA
Other	257 (6)	NA
Positive for hepatitis C infection	668 (17)	–

* HIV = human immunodeficiency virus; NA = not available.

Approvals and Permissions

The Danish Data Protection Agency approved the establishment of the cohort study. The study was not subject to approval by the ethics committee because data collection did not involve direct patient contact.

Role of the Funding Sources

The Danish HIV Cohort study receives funding from the Danish AIDS Foundation, Odense University Hospital, Preben and Anna Simonsen's Foundation, the Foundation of the Danish Association of Pharmacists, and the Clinical Institute at the University of Southern Denmark. The funding sources were not involved in the design, data collection, analysis, or writing of the study.

RESULTS

Study Sample

We included 3990 HIV-infected persons and 379 872 persons from the general population: The respective median observation time after age 25 years was 5.8 person-years (interquartile range, 2.2 to 9.9 person-years) and 8.4 person-years (interquartile range, 4.3 to 10.3 person-years), respectively (**Table 1**). One hundred twenty-one (3.0%) HIV-infected patients and 11 552 (3.0%) persons from the general population were lost to follow-up; of these, 107 (2.7%) patients with HIV infection and 10 234 (2.7%) persons from the general population emigrated. There were 2045 (51%) incident HIV cases diagnosed after 1 January 1995; 75% were observed within 31 days of diagnosis, and 95% came under observation within the first 181 days after diagnosis. After HAART was introduced in 1996, the prevalence of patients receiving this treatment gradually increased, surpassing 75% in 2002 to 2004. At any given time, fewer than 5% of HIV-infected patients were interrupting treatment. The number of patients under observation varied with age and was highest (range, 515 to 1004) for those who were 30 to 50 years of age (**Table 2**).

Survival from Age 25 Years

All participants were observed from age 25 years: HIV-infected persons had a median survival of 19.9 years (17.5 years for men and 24.2 years for women), whereas persons from the general population had a median survival of 51.1 years (50.8 years for men and 54.8 years for women) (**Table 3**). During the late HAART period (2000 to 2005), median survival of HIV-infected patients had increased to 32.5 years (32.1 years for men and 32.3 years for women) overall, and to 38.9 years (37.8 years for men and 40.1 years for women) after persons with known HCV infection were excluded (**Figure**).

Mortality Rates

The mortality rate was 43 per 1000 person-years (95% CI, 40 to 45) for HIV-infected persons and 4.7 per 1000 person-years (CI, 4.6 to 4.8) for the general population (**Table 3**). The highest mortality rate, 124 per 1000 person-years (CI, 112 to 137), was observed in the pre-HAART period (1995 to 1996). This rate decreased to 38 per 1000 person-years (CI, 33 to 43) in the early HAART period (1997 to 1999) and to 25 per 1000 person-years (CI, 23 to 28) in the late HAART period (2000 to 2005). In patients receiving HAART, the highest mortality rate of 48 per 1000 person-years (CI, 40 to 57) was observed during the first year of treatment but decreased to 27 per 1000 person-years (CI, 22 to 32) during the second and third years of HAART, to 26 per 1000 person-years (CI, 21 to 32) during the fourth and fifth years of HAART, and to 26 per 1000 person-years (CI, 21 to 31) from the sixth year onward. Mortality rates were even lower among patients treated during the late HAART period. Although mortality rates declined with calendar time, we found no change in mortality rates from the first to the tenth year after the diagnosis of HIV infection. In the late HAART period, the mortality rate was 26 per 1000 person-years (CI, 19 to 34) during the first 2 years after diagnosis, 17

Table 2. **Age-Specific Mortality Rates***

Variable	Age			
	25–30 y	>30–35 y	>35–40 y	>40–45 y
Under observation at the beginning of each age period, *n*				
Patients with HIV infection	170	566	959	950
General population	17 045	60 322	107 786	112 343
PYR (in thousands), *n*				
Patients with HIV infection	1.77	3.97	4.92	4.13
General population	184	432	567	505
Events, *n*				
Patients with HIV infection	54	113	176	189
General population	128	385	761	1296
Mortality rate for patients with HIV infection, per 1000 PYR	30.5 (23.4 to 39.9)	28.5 (23.7 to 34.3)	35.8 (30.8 to 41.4)	45.7 (39.7 to 52.7)
Mortality rate for general population, per 1000 PYR	0.7 (0.6 to 0.8)	0.9 (0.8 to 1.0)	1.3 (1.3 to 1.4)	2.6 (2.4 to 2.7)
Mortality rate ratio (patients vs. general population)	44.53 (32.0 to 61.9)	32.04 (25.9 to 39.7)	27.4 (23.1 to 32.4)	18.04 (15.4 to 21.1)
Excess mortality rate (patients vs. general population, per 1000 PYR)	29.8 (21.7 to 38.0)	27.6 (22.3 to 32.9)	34.4 (29.1 to 39.7)	43.2 (36.6 to 49.7)
Patients observed during the years 2000–2005				
Patients with HIV infection, PYR (in thousands)	0.77	1.98	3.04	2.58
Mortality rate for patients with HIV infection, per 1000 PYR	6.5 (2.7 to 15.6)	11.6 (7.7 to 17.5)	17.4 (13.3 to 22.8)	24.0 (18.7 to 30.8)
Mortality rate for general population, per 1000 PYR	0.6 (0.5 to 0.8)	0.8 (0.7 to 0.9)	1.2 (1.1 to 1.3)	2.3 (2.1 to 2.4)
Mortality rate ratio (patients vs. general population)	8.88 (3.2 to 24.7)	15.14 (9.7 to 23.5)	14.36 (10.7 to 19.3)	10.55 (8.1 to 13.8)
Excess mortality rate (patients vs. general population), per 1000 PYR	5.8 (1.6 to 11.5)	10.9 (6.1 to 15.6)	16.2 (11.5 to 20.9)	21.8 (15.8 to 27.8)
HCV-negative patients observed during the years 2000–2005				
Patients with HIV infection, PYR (in thousands)	0.67	1.66	2.45	1.99
Mortality rate for patients with HIV infection, per 1000 PYR	1.5 (0.2 to 10.6)	8.5 (5.0 to 14.3)	13.5 (9.6 to 19.0)	14.1 (9.7 to 20.4)
Mortality rate for general population, per 1000 PYR	0.6 (0.5 to 0.8)	0.8 (0.7 to 0.9)	1.2 (1.1 to 1.3)	2.3 (2.1 to 2.5)
Mortality rate ratio (patients vs. general population)	2.6 (0.4 to 19.3)	10.7 (6.2 to 18.6)	11.5 (8.0 to 16.6)	6.3 (4.3 to 9.3)
Excess mortality rate (patients vs. general population), per 1000 PYR	0.9 (−2.1 to 3.8)	7.7 (3.2 to 12.1)	12.3 (7.7 to 16.9)	11.8 (6.5 to 17.0)
HCV-positive patients observed during the years 2000–2005				
Patients with HIV infection, PYR (in thousands)	0.10	0.32	0.59	0.59
Mortality rate for patients with HIV infection, per 1000 PYR	38.5 (14.5 to 102.7)	28.2 (14.7 to 54.2)	33.7 (21.7 to 52.2)	57.8 (41.3 to 81.0)
Mortality rate for general population, per 1000 PYR	0.8 (0.4 to 1.6)	0.7 (0.5 to 1.0)	1.3 (1.1 to 1.6)	2.1 (1.8 to 2.5)
Mortality rate ratio (patients vs. general population)	41.6 (10.8 to 160.9)	42.1 (19.2 to 92.6)	24.5 (14.8 to 40.6)	24.4 (16.6 to 35.8)
Excess mortality rate (patients vs. general population), per 1000 PYR	37.8 (0.0 to 75.5)	27.5 (9.1 to 46.0)	32.4 (17.6 to 47.2)	55.7 (36.3 to 75.2)

* Values in parentheses are 95% CIs. HCV = hepatitis C virus; HIV = human immunodeficiency virus; NA = not available; PYR = person-years at risk.

per 1000 person-years (CI, 12 to 24) during the third and fourth years, 18 per 1000 person-years (CI, 13 to 25) during the fifth and sixth years, 21 per 1000 person-years (CI, 15 to 29) during the seventh and eighth years, and 17 per 1000 person-years (CI, 11 to 25) during the ninth and tenth years after diagnosis. Persons with HIV and HCV coinfection had considerably higher mortality rates than those who were HCV-negative (mortality rate, 59 [CI, 52 to 67] vs. 39 [CI, 36 to 42]), and this finding was even more marked in the late HAART period (mortality rate, 57 [CI, 48 to 67] vs. 19 [CI, 17 to 22]).

Age-Specific Mortality Rates

Mortality rates increased with age for HIV-infected persons and for the general population (**Table 2**). Among HCV-negative persons with HIV infection who were younger than 50 years, mortality rates during the late HAART period did not exceed 15.0 per 1000 person-years (CI, 10.0 to 22.6).

The mortality rates for HIV-infected persons relative to those for the general population (mortality rate ratio) were highest in the younger age groups. The decrease in mortality rate ratio with age was driven by the natural age-dependent increase in mortality rates in the reference population. The mortality rate ratio decreased from 44.5 (CI, 32.0 to 61.9) for persons who were age 25 to 30 years to 3.4 (CI, 2.3 to 5.1) for those who were age 65 to 70 years. Among persons observed in the late HAART period, the mortality rate ratio varied from 15.1 (CI, 9.7 to 23.5) to 3.0 (CI, 2.0 to 4.6) for all HIV-infected patients. After HCV-positive persons were excluded, the mortality rate ratio during this period ranged from 11.5 (CI, 8.0 to 16.6) to 2.8 (CI, 2.0 to 4.0).

In contrast to the age-related decrease in mortality rate ratio, the excess mortality rate for HIV-infected patients compared with that for the general population was lowest in the younger age groups and increased with age. The

Table 2—**Continued**

Age				
>45–50 y	>50–55 y	>55–60 y	>60–65 y	>65–70 y
727	517	373	224	77
90 759	65 254	45 872	27 170	11 023
3.07	2.26	1.53	0.67	0.28
386	280	185	86	40
155	111	69	49	26
1795	2036	2031	1543	1169
50.5 (43.1 to 59.1)	49.2 (40.8 to 59.2)	45.2 (35.7 to 57.3)	73.4 (55.4 to 97.1)	93.1 (63.4 to 136.7)
4.7 (4.4 to 4.9)	7.3 (7.0 to 7.6)	11.0 (10.5 to 11.4)	18.0 (17.1 to 18.9)	29.1 (27.5 to 30.8)
10.81 (9.1 to 12.8)	7.24 (6.0 to 8.8)	4.05 (3.2 to 5.2)	4.23 (3.2 to 5.6)	3.43 (2.3 to 5.1)
45.9 (37.9 to 53.8)	41.9 (32.7 to 51.0)	34.3 (23.6 to 45.0)	55.4 (34.8 to 75.9)	64.0 (28.2 to 99.8)
1.93	1.40	1.14	0.51	0.18
32.2 (25.1 to 41.3)	33.5 (25.2 to 55.6)	34.3 (25.0 to 46.9)	49.3 (33.3 to 73.0)	81.3 (49.1 to 134.9)
4.5 (4.3 to 4.8)	7.1 (6.7 to 7.5)	10.6 (10.0 to 11.1)	17.0 (16.1 to 18.1)	28.5 (26.6 to 30.5)
6.81 (5.2 to 8.9)	5.14 (3.8 to 7.0)	3.16 (2.3 to 4.4)	3.04 (2.0 to 4.6)	3.11 (1.9 to 5.2)
27.6 (19.6 to 35.7)	26.4 (16.8 to 36.0)	23.7 (12.9 to 34.4)	32.3 (12.9 to 51.6)	52.8 (11.7 to 94.0)
1.53	1.22	1.10	0.49	0.18
15.0 (10.0 to 22.6)	27.8 (19.9 to 39.0)	30.1 (21.4 to 42.4)	47.0 (31.3 to 70.8)	82.3 (49.6 to 136.5)
4.6 (4.3 to 4.9)	7.0 (6.6 to 7.5)	10.6 (10.0 to 11.2)	17.0 (16.0 to 18.1)	28.5 (26.6 to 30.5)
3.0 (2.0 to 4.7)	4.3 (3.1 to 6.2)	2.8 (2.0 to 4.0)	3.0 (2.0 to 4.6)	3.1 (1.9 to 5.2)
10.4 (4.3 to 16.6)	20.8 (11.4 to 30.2)	19.5 (9.2 to 29.8)	30.0 (10.8 to 49.3)	53.8 (12.1 to 95.5)
0.40	0.18	0.04	0.02	0.00
98.5 (72.0 to 134.8)	71.3 (41.4 to 122.7)	141.3 (63.5 to 314.6)	109.9 (27.5 to 439.3)	NA
4.3 (3.8 to 4.9)	7.3 (6.4 to 8.3)	10.1 (8.0 to 12.8)	17.3 (13.0 to 23.0)	27.9 (20.4 to 38.0)
21.6 (15.2 to 30.8)	10.3 (5.7 to 18.8)	13.7 (5.3 to 35.5)	3.5 (0.5 to 26.0)	NA
94.2 (63.3 to 125.1)	64.0 (25.2 to 102.8)	131.2 (18.1 to 244.3)	92.6 (−59.8 to 244.9)	NA

excess mortality rate during the late HAART period was not higher than 12.3 per 1000 person-years (CI, 7.7 to 16.9) among HCV-negative persons who were younger than 50 years but increased gradually with age to 53.8 per 1000 person-years (CI, 12.1 to 95.5) among persons who were 65 to 70 years. These figures were 2- to 4-fold higher if all patients and observation years were included (**Table 2**).

Causes of Death

The mortality rate for HIV-related death decreased from 71 per 1000 person-years (CI, 63 to 81) in the early HAART period to 7.0 per 1000 person-years (CI, 5.8 to 8.6) in the late HAART period, and non–HIV-related deaths decreased from 23 per 1000 person-years (CI, 18 to 29) to 9.4 per 1000 person-years (CI, 7.9 to 11.2) (**Table 4**). Thus, the proportion of known causes of death that were related to HIV infection decreased from 76% in 1995 to 1996, to 57% in 1997 to 1999, and to 43% in 2000 to 2005.

Discussion

In this population-based cohort study, we estimate a median remaining lifetime of more than 35 years for a 25-year-old, HIV-positive person without HCV infection who received care in the twenty-first century. We expect this estimate to be robust because the study included all patients, regardless of such prognostic factors as CD4-positive cell count, HIV RNA, disease stage, history of AIDS, treatment adherence, or time receiving HAART. The increase in survival over time was attributable mainly to a decrease in HIV-related deaths. Despite the encouraging survival expectations, the study still shows large, age-dependent excess mortality rates in the HIV-infected cohort compared with the general population. The excess mortal-

Table 3. **Median Survival and Mortality Rates Starting at Age 25 Years***

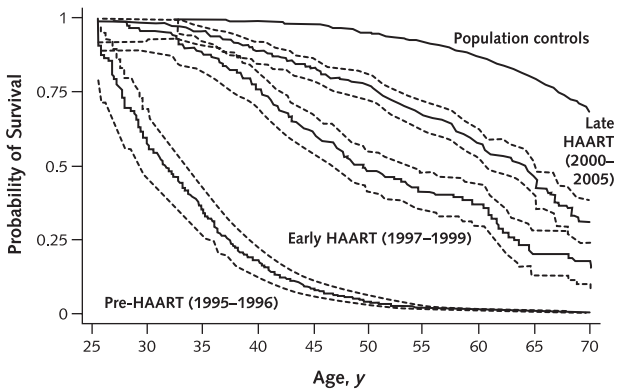
Variable	PYR	Events	Mortality Rate per 1000 PYR (95% CI)			Median Survival after Age 25 Years (95% CI), *y*		
			Total	Men	Women	Total	Men	Women
General population	2 689 287	12 565	4.7 (4.6–4.8)	5.5 (5.4–5.6)	1.8 (1.7–1.9)	51.1 (50.9–51.5)	50.8 (50.4–51.1)	54.8 (53.4–∞)
Patients with HIV infection	22 744	970	43 (40–45)	47 (44–50)	29 (25–34)	19.9 (18.5–21.3)	17.5 (15.4–19.3)	24.2 (21.6–26.6)
HAART period								
No HAART	8271	537	65 (60–71)	75 (68–82)	37 (30–46)			
1st year	2605	124	48 (40–57)	51 (42–62)	35 (23–54)			
2nd–3rd year	4534	121	27 (22–32)	28 (23–35)	21 (14–32)			
4th–5th year	3570	92	26 (21–32)	26 (21–33)	25 (16–39)			
6th year onward	3764	96	26 (21–31)	27 (22–34)	18 (11–31)			
Time since diagnosis								
1st–2nd years after diagnosis	3436	159	46 (40–54)	53 (44–62)	28 (19–42)			
3rd–4th years after diagnosis	3419	133	39 (33–46)	44 (36–53)	25 (17–38)			
5th–6th years after diagnosis	3136	116	37 (31–44)	40 (33–50)	28 (19–42)			
7th–8th years after diagnosis	2799	117	42 (35–50)	47 (39–58)	26 (16–41)			
9th–10th years after diagnosis	2614	129	49 (42–59)	56 (46–67)	30 (19–47)			
Hepatitis C status								
Positive	4149	246	59 (52–67)	68 (59–78)	44 (34–56)	17.6 (15.0–19.6)	15.3 (10.3–18.1)	21.6 (17.4–24.2)
Negative	18 595	724	39 (36–42)	43 (40–46)	24 (19–29)	21.0 (19.3–23.2)	18.5 (16.0–20.6)	27.4 (23.6–35.0)
Observation period								
1995–1996	3243	402	124 (112–137)	136 (122–151)	78 (60–103)	7.6 (4.8–9.6)	5.5 (3.4–8.5)	11.0 (6.3–12.9)
1997–1999	5857	222	38 (33–43)	41 (35–47)	28 (20–38)	22.5 (20.0–24.5)	22.1 (18.2–24.0)	24.6 (16.6–36.4)
2000–2005	13 644	346	25 (23–28)	27 (24–30)	20 (16–26)	32.5 (29.4–34.7)	32.1 (28.5–34.9)	32.3 (24.5–36.1)
Patients with HIV infection observed 2000–2005 only								
HAART period								
No HAART	2946	66	22 (18–29)	26 (20–34)	15 (9–26)			
1st year	1073	46	43 (32–57)	50 (37–69)	24 (11–50)			
2nd–3rd year	2464	57	23 (18–30)	23 (17–31)	23 (14–38)			
4th–5th year	3398	81	24 (19–30)	24 (18–30)	24 (15–38)			
6th year onward	3763	96	26 (21–31)	27 (22–34)	18 (11–31)			
Time since diagnosis								
1st–2nd years after diagnosis	1875	48	26 (19–34)	30 (22–40)	15 (8–31)			
3rd–4th years after diagnosis	1901	32	17 (12–24)	17 (11–26)	16 (9–32)			
5th–6th years after diagnosis	1786	32	18 (13–25)	16 (11–25)	22 (12–40)			
7th–8th years after diagnosis	1630	34	21 (15–29)	23 (16–33)	16 (7–33)			
9th–10th years after diagnosis	1439	24	17 (11–25)	18 (12–29)	12 (5–30)			
Hepatitis C status								
Positive	2245	127	57 (48–67)	59 (48–74)	52 (38–70)	19.6 (16.1–21.9)	19.3 (9.6–22.2)	21.1 (14.9–23.7)
Negative	11 399	219	19 (17–22)	22 (19–25)	10 (7–15)	38.9 (35.4–40.1)	37.8 (34.3–40.0)	40.1 (35.0–∞)

* HAART = highly active antiretroviral therapy; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PYR = person-years at risk.

ity rates increased with increasing age, whereas the relative mortality rates decreased.

Three previous studies have compared age- sex- and calendar-year–specific mortality rates of HIV-infected patients with those of the general population (2, 3, 14). In the Dutch ATHENA (AIDS Therapy Evaluation, the Netherlands Study Group) cohort (2), the overall mortality rate among HIV-infected patients was considerably lower (10.6 per 1000 person-years) than in our study; as in our study, the ATHENA cohort showed a pattern of decreasing relative mortality rates with increasing age but no increase in the excess mortality rate with age. However, the study sample was restricted to antiretroviral-naive patients who had survived the first 24 weeks of a HAART regimen. In contrast, we included all patients, both those who were diagnosed with advanced disease and did not survive for 24 weeks and those who did not yet meet the criteria for HAART, which allowed us to estimate survival in the total HIV population. In the Swiss HIV Cohort Study, Jaggy and colleagues (14) studied excess mortality rates in pa-

Figure. **Survival from age 25 years.**



Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. Dashed lines indicate 95% CIs. HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy.

tients "successfully treated with HAART" (excess mortality rate, 3.1 to 8.0 [HCV-negative] and 20.5 to 25.9 [HCV-positive] per 1000 person-years) vs. "unsuccessfully treated with HAART" (excess mortality rate, 117.4 [HCV-negative] and 112.7 [HCV-positive] per 1000 person-years). These authors did not report the distribution of ages in their study groups or the age-specific excess mortality rates. In another analysis based on the Swiss HIV Cohort Study, Keiser and colleagues (3) found a decrease in the mortality rate from 130 per 1000 person-years during 1990 to 1995 to 30 per 1000 person-years during 1997 to 2001, and a concomitant decrease in standardized mortality rate ratio from 79.3 to 15.3. There was a 21% withdrawal rate in that study, and no information was available regarding participants' age distributions. Because mortality rates among HIV-infected and noninfected persons are highly age-dependent, the age-specific mortality rates reported in our study allow transparency and easier comparison among studies and samples. Further, the 2 Swiss Cohort Study reports were based on data up to 2001 and did not incorporate the advances in treatment effectiveness obtained during the subsequent 4 years. Braithwaite and coworkers (15) used data from the Collaborations in HIV Outcomes Research/US (CHORUS) cohort (16) to develop a computer model that incorporated time-updated CD4-positive cell counts, viral load, adherence to treatment, and development of resistance; the estimated median survival from that model was 20.4 years for newly diagnosed patients. Compared with CHORUS, which is a clinic-based, multistate cohort study requiring informed consent from the patients, DHCS is geographically based with almost complete inclusion of HIV-infected patients in our area. Therefore, we may interpret our findings as a result of the total health care effort in our area.

The mortality rates for HIV-infected patients may be put into clinical perspective by comparison with mortality rates among patients with type 1 diabetes mellitus, another serious chronic disease of young adults. Laing and coworkers (17) estimated age- and sex-specific mortality rates for patients with type 1 diabetes (per 1000 person-years). They reported the following mortality rates for women and men, respectively: for age 30 to 39 years, 3.2 and 4.2; for age 40 to 49 years, 8.5 and 11.6; for age 50 to 59 years, 19.1 and 26.2; and for age 60 to 69 years, 44.6 and 63.2. These rates are slightly lower than the rates we found among persons without HCV infection during the late HAART era.

The strengths of our study are its population-based setting, minimal participants lost to follow-up, high quality of the death registration (that is, we are certain that all

Table 4. **Mortality Rates according to Cause of Death and Calendar Period***

Observation Period	Cause of Death	PYR, *n*	Events, *n*	Mortality Rate per 1000 PYR (95% CI)	All-Cause Mortality Rate, %	Mortality Rate by Known Causes, %
1995–1996						
	All causes	3243	402	124 (112–137)	100	
	HIV-related	3243	231	71.2 (62.6–81.0)	57	76
	Non–HIV-related	3243	75	23.1 (18.4–29.0)	19	24
	Unknown	3243	96	29.6 (24.2–36.2)	24	
1997–1999						
	All causes	5857	222	37.9 (33.2–43.2)	100	
	HIV-related	5857	104	17.8 (14.7–21.5)	47	57
	Non–HIV-related	5857	80	13.7 (11.0–17.0)	36	43
	Unknown	5857	38	6.5 (4.7–8.9)	17	
2000–2005						
	All causes	13 644	346	25.4 (22.8–28.2)	100	
	HIV-related	13 644	96	7.0 (5.8–8.6)	28	43
	Non–HIV-related	13 644	128	9.4 (7.9–11.2)	37	57
	Unknown	13 644	122	8.9 (7.5–10.7)	35	

* HIV = human immunodeficiency virus; PYR = person-years at risk.

dates were correct for all registered deaths), clearly defined date of inclusion of all prevalent and incident cases of HIV infection in Denmark (1 January 1995), and large proportion of incident cases observed shortly after patients were diagnosed with HIV infection, which allowed us to follow up on most patients from before initiation of HAART.

Despite the advantages of good-quality data, our study has limitations. First, survival predictions were based on the assumption that the observed mortality rates also would apply in subsequent years, whereas actual observation time of any individual patient was at most 10 years. However, we found no increase in mortality rates through the first 10 years of infection or increase in mortality rates with increasing time receiving HAART, and we found a decrease in mortality rates with increasing calendar period. These findings agree with a previous study from DHCS, in which we observed a decreasing incidence of triple-class drug failure with successive calendar periods (18). Thus, we did not see any signs of waning effectiveness of HAART, which is currently debated and considered to be a potential health threat because of multiclass drug failure, accumulation of drug resistance, and long-term drug toxicities (19, 20) Although our predictions reach far beyond the current experience with HIV and HAART, we saw no signs that a 50-year-old patient who was infected several years previously had a higher mortality rate than a recently infected 50-year-old patient. Second, some eligible HIV-infected persons may not have been included in the study. Because dispensing antiretroviral drugs in Denmark is restricted to HIV clinics and is free, many of the missed patients are probably those who do not fulfill the criteria for HAART and therefore have low mortality rates. This would cause overestimation of mortality rates in the HIV-infected cohort. In contrast, many patients may not seek care despite being eligible for antiretroviral treatment and may belong to a group with such comorbid conditions as mental health disorders or addiction problems. This group would have a higher risk for death, because of HIV infection and comorbid conditions, thus leading to an underestimation of the mortality rates in the HIV-infected cohort. Third, the HIV-infected population is thought to differ from the general population regarding socioeconomic and behavioral factors (8, 21) and having acquired HIV infection probably indicates a tendency toward risk behaviors. Studies have shown a higher frequency of smoking and alcohol consumption among HIV-infected patients (22, 23). Matching the cohort of persons from the general population according to sex, age, and place of residence may partly correct for these group differences, but any residual confounding by lifestyle or comorbid conditions would cause an overestimation of the observed excess mortality rates because of HIV infection. Fourth, the results are influenced by the composition of the study sample. In our cohort, and in most other HIV-infected populations, the mortality rates differ in subgroups (defined by HCV coinfection status, ethnicity, risk behaviors, and sex), and may be influenced by the person's position on different time scales (age, time receiving HAART, and calendar time). To explore and clarify the effect of these covariates, we presented mortality rates in selected time strata. The subgroup with the best prognosis (persons without HCV coinfection) comprised 84% of all persons observed in the late HAART era and was therefore chosen as a clinically useful reference group.

The survival projections in our study depend on continuous treatment success beyond the 10 years of current experience with HAART. Further, with the easy access to HAART and HIV care in Denmark, our findings may represent a best-case scenario. Not all subgroups of patients have the same prognosis, and treatment must be individualized according to actual risk estimates. Our study suggests that most young persons with HIV infection can expect to survive for more than 35 years, but an ongoing effort is still needed to further reduce mortality rates in these persons.

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MAJOR ARTICLE

Mortality in Siblings of Patients Coinfected with HIV and Hepatitis C Virus

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(See the editorial commentary by Tillmann and Thursz, on pages 168–70.)

Background. Coinfection with hepatitis C virus (HCV) is a poor prognostic factor for human immunodeficiency virus (HIV)–infected patients. We examined whether the increased mortality in these patients is partly explained by a familial excess risk of death.

Methods. Danish HIV-infected patients who had had at least 1 HCV test were included ($n = 3531$). In addition, 336,652 population control subjects matched for sex, age, and residency were identified from the Danish Civil Registration System. For both HIV-infected patients and population control subjects, we identified all siblings born after 1951, with dates of death or emigration. Siblings of HIV-infected patients were classified according to the patients' HCV serostatus. Survival after age 20 years was compared among the groups of siblings.

Results. We identified 437 siblings of HIV/HCV-coinfected patients, 1856 siblings of HIV-monoinfected patients, and 285,509 siblings of population control subjects. Mortality was substantially higher in siblings of HIV/HCV-coinfected patients than in either siblings of HIV-monoinfected patients (mortality rate ratio [MRR], 2.97 [95% confidence interval {CI}, 1.98–4.45]) or siblings of control subjects (MRR, 4.23 [95% CI, 3.09–5.79]). Siblings of HIV-monoinfected patients had slightly higher mortality (MRR, 1.43 [95% CI, 1.10–1.85]) than siblings of control subjects.

Conclusions. HCV infection is a marker of familial factors that affect the survival of HIV-infected patients independently of the pathogenicity of HCV.

Approximately 30% of HIV-infected patients in Western countries are coinfected with hepatitis C virus (HCV) [1, 2]. Most large cohort studies have shown increased liver-related mortality in coinfected patients [1, 3, 4], compared with HIV-monoinfected patients. Data are conflicting regarding non–liver-related mortality. Some studies have found increased mortality from causes unrelated to liver disease [3, 4], whereas others have not [5, 6]. Still other studies have reported a higher incidence of AIDS-defining events and death among HCV-coinfected patients, but the effect disappeared after other prognostic factors and time receiving highly active antiretroviral therapy (HAART) were taken into account [1, 7]. In the Danish HIV Cohort Study (DHCS), overall mortality among HCV-coinfected patients was 2.4-fold higher than that among HIV-monoinfected patients [4]. This excess mortality was only partially attributable to liver disease, and the excess mortality from other causes persisted after adjustment for available covariates.

The impact of HCV on the clinical course of HIV or the response to HAART [8–10] remains unclear. It also is not known whether increased mortality in HIV/HCV-coinfected patients is partly explained by other factors. We hypothesized that HIV/HCV coinfection is a marker for familial risk factors that affect survival in HIV-infected patients independently of the pathoge-

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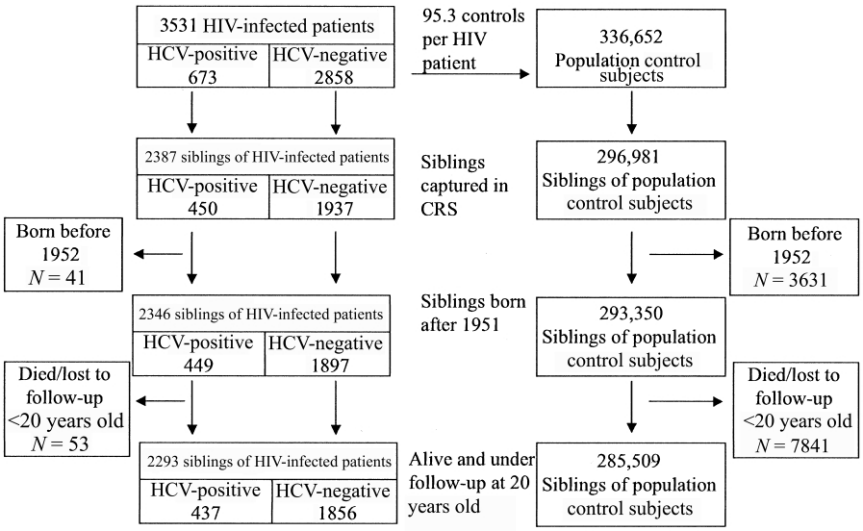

Figure 1. Summary of the study design. CRS, Danish Civil Registration System; HCV, hepatitis C virus.

nicity of HCV. To examine this hypothesis, we compared mortality in 3 groups: siblings of patients coinfected with HIV and HCV, siblings of HIV-monoinfected patients, and siblings of HIV-negative population control subjects.

SUBJECTS AND METHODS

HIV-infected patients. The DHCS, which has been described elsewhere [11], encompasses all HIV-infected patients treated in Danish HIV clinics since 1 January 1995. As of 1 May 2005, the cohort included 4261 Danish residents who were >16 years old at the time of HIV diagnosis. We excluded 271 patients not living in Denmark at the time of HIV diagnosis and 459 patients who were never tested for HCV. The remaining 3531 HIV-infected patients were included in the study and classified into 2 groups according to HCV status: (1) patients with HIV and at least 1 serological test positive for HCV and/or with HCV RNA detected (HIV/HCV-coinfected patients) and (2) HIV patients with at least 1 negative serological test for HCV and no history of a positive test (HIV-monoinfected patients).

Population control subjects. Using the Danish Civil Registration System (CRS) [12], we aimed to identify 99 population control subjects for each HIV-positive patient. The CRS, a computerized registry established in 1968, uses a unique 10-digit civil registration number to store data about birth, sex, residency, date of immigration or emigration, date of death, date of disappearance (loss to follow-up), and kinship (parents and children) for each Danish resident. Control subjects had to be alive and living in the same municipality as the HIV-infected patient on the date when HIV was diagnosed (1 January 1995 was used for patients with an earlier date of diagnosis). Control subjects were matched to patients by sex and age.

Siblings. For both HIV-infected patients and population control subjects, we identified all registered full siblings (i.e., siblings with the same biological mother and father). We retrieved data on siblings' birth dates, emigration, and loss to follow-up. Over time, inclusion of parents' civil registration numbers in the CRS has increased from <10% for individuals born before 1952, to 43% for the 1952 birth cohort, to 96% for the 1959 birth cohort, and to 99% for persons born after 1970 [13]. Consistent with this trend, we found that <7% of individuals born before 1952 had registered siblings. Thus, to reduce selection bias, siblings born before 1 January 1952 were excluded from the study. Siblings of HIV-infected patients were classified according to the patients' HCV status as siblings of HIV/HCV-coinfected patients and those of HIV-monoinfected patients.

Mortality. For siblings of HIV-infected patients and siblings of population control subjects, we computed time from age 20 years until death. Siblings were censored at emigration, loss to follow-up, 1 May 2005, or their 50th birthday, whichever came first. Siblings were censored at age 50 years because of the relatively few person-years of follow-up after this age.

Statistical analysis. The demographic characteristics of siblings were compared using the χ^2 and Kruskal-Wallis tests as appropriate. $P < .05$ was considered to be significant. If the comparison of the 3 groups was significant, we proceeded to test pairwise comparisons of siblings of HIV/HCV-coinfected patients with both siblings of HIV-monoinfected patients and siblings of population control subjects.

We computed mortality rates for 10-year age intervals using life tables and constructed Kaplan-Meier survival curves for the 3 sibling groups (siblings of HIV/HCV-coinfected patients, siblings of HIV-monoinfected patients, and siblings of control subjects). We used Cox proportional-hazards regression to es-

timate mortality rate ratios (MRRs) and to adjust for siblings' sex and birth year (to adjust for a potential birth cohort effect). Birth year was divided into 3 categories: 1952–1961, 1962–1971, and 1972 and later.

We observed almost identical mortality among siblings of population control subjects, regardless of HCV status in the matched HIV patients (MRR, 1.04 [95% confidence interval {CI}, 0.98–1.11]). For this reason, control siblings for both the HIV/HCV-coinfected and HIV-monoinfected patients were combined into a single group in all analyses.

Cox regression analyses were repeated in the following subgroups: siblings born in Denmark, oldest siblings, youngest siblings, siblings of patients with sexually transmitted HIV, siblings of HIV-infected patients without hemophilia, and a group excluding siblings known to be HIV infected. Furthermore, we stratified the analyses by history of intravenous drug use (IDU) in the index patients (defined as having acquired HIV through IDU). To assess bias potentially introduced by disregarding matching, we recalculated our MRR estimates for the main comparison of mortality rates in siblings of HIV/HCV-coinfected patients, siblings of HIV-monoinfected patients, and siblings of population control subjects, stratifying on matched sets, and we found <7% deviation from results obtained in the unmatched analysis. The proportional-hazards assumptions were assessed graphically and found to be appropriate. We used SPSS (version 12.01, Norusis; SPSS) and Stata (version 8.2; StataCorp) software. The study was approved by the Danish Data Protection Agency.

RESULTS

Study population. Of the 3531 HIV-infected patients, 2858 were HCV negative and 673 were HCV positive. These patients had 2387 siblings registered in the CRS. Owing to an insufficient number of eligible control subjects in some municipalities, the study included a mean of 95.3 population control subjects per HIV-infected patient, yielding 336,652 matched control subjects with 296,981 registered siblings (figure 1).

HIV/HCV-coinfected patients and HIV-monoinfected patients had fewer registered siblings per individual (0.67 and 0.68, respectively) than did population control subjects (0.88). Among Danish-born individuals, the figures were 0.70 siblings per HIV/HCV-coinfected individual, 0.79 siblings per HIV-monoinfected individual, and 0.90 siblings per population control subject.

After excluding siblings born before 1952 and siblings who died or were lost to follow-up before they were 20 years old, 2293 siblings of HIV-infected patients and 285,509 siblings of population control subjects were available for analysis. The 2293 siblings of HIV-infected patients contributed 45,670 person-years of follow-up, counting from age 20 to 50 years; 97 (4.2%) died, and 74 (3.2%) were censored before 1 May 2005 because of emigration (72 [3.1%]) or loss to follow up (2 [0.1%]). The control siblings provided 5,511,792 person-years of follow-up; 5924 (2.1%) died, and 10,272 (3.6%) were censored because of emigration (10,034 [3.5%]) or loss to follow-up (238 [0.1%]) (table 1).

Although 17% of HIV-infected patients and 7% of population control subjects were born outside Denmark, few of them had siblings residing in Denmark. Siblings of HIV/HCV-coinfected patients were somewhat more likely than siblings of HIV-monoinfected patients to be born outside Denmark (4.6% vs. 1.0%) (table 1). There was a strong association between IDU and HCV infection: 63% of HIV/HCV-coinfected patients had

Table 1. Characteristics of siblings.

Siblings[a]	Siblings of HIV/HCV-coinfected patients (n = 437)	Siblings of HIV-monoinfected patients (n = 1856)	Siblings of population control subjects (n = 285,509)	P
Year of birth, median (IQR)	1964 (1959–1968)	1963 (1959–1968)	1965 (1960–1970)	.92,[b] .007[c]
Born in Denmark, no. (%)	417 (95.4)	1837 (99.0)	281,860 (98.7)	<.001,[b] <.001[c]
Mode of HIV transmission,[d] no. (%)				
IDU	293 (67)	24 (1)	NA	<.001[b]
Hemophilia	35 (8)	0		<.001[b]
Died between age 20 and 50 years, no. (%)	39 (8.9)	58 (3.1)	5924 (2.1)	
Emigrated, no. (%)	11 (2.5)	61 (3.3)	10,034 (3.5)	
Lost to follow-up, no. (%)	0	2 (0.1)	238 (0.1)	
Person-years of follow-up	8533	37,137	5,511,792	

NOTE. HCV, hepatitis C virus; IDU, intravenous drug use; IQR, interquartile range; NA, not applicable.

[a] Born after 1951, alive, and under follow-up at age 20 years.
[b] Siblings of HIV/HCV-coinfected patients vs. siblings of HIV-monoinfected patients.
[c] Siblings of HIV/HCV-coinfected patients vs. siblings of population control subjects.
[d] Refers to the related HIV-infected patient.

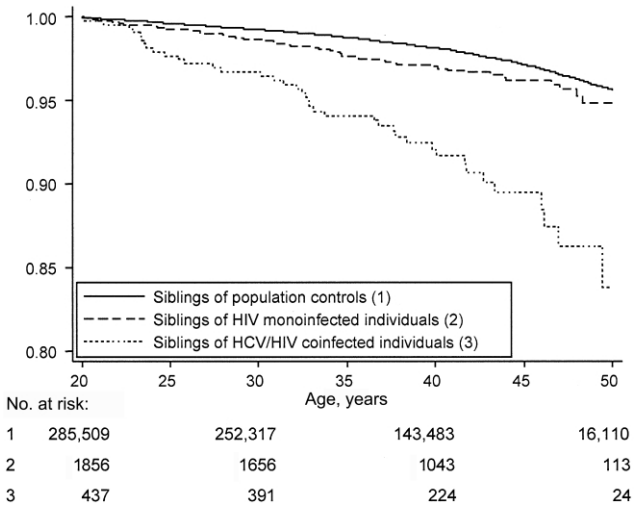

Figure 2. Kaplan-Meier curve of the probability of remaining alive in the 3 groups of siblings: siblings of population control subjects, siblings of HIV-monoinfected patients, and siblings of HIV/hepatitis C virus (HCV)–coinfected patients.

acquired HIV through IDU, and 95% of injection drug users were HCV seropositive.

Nine families included 2 siblings with HIV. Hence, 18 persons (0.8%) were included as both HIV-infected patients and siblings of HIV-infected patients. Six of them—all coinfected with HCV—died during follow-up. Among control siblings, 397 (0.1%) were registered in DHCS as having HIV infection; of these, 74 died during follow-up.

Mortality. We found higher mortality among siblings of HIV/HCV-coinfected patients than among siblings of both HIV-monoinfected patients (MRR, 2.97 [95% CI, 1.98–4.45]) and population control subjects (MRR, 4.23 [95% CI, 3.09–5.79]). Compared with siblings of population control subjects, siblings of HIV-monoinfected patients had modestly higher mortality (MRR, 1.43 [95% CI, 1.10–1.85]) (figure 2; table 2).

Sensitivity analysis. The exclusion of HIV-infected siblings yielded slightly lower estimates: MRR, 2.61 (95% CI, 1.70–4.00) for siblings of HIV/HCV-coinfected patients, compared with siblings of HIV-monoinfected patients, and MRR, 3.77 (95% CI, 2.68–5.30) for siblings of HIV/HCV-coinfected patients, compared with siblings of population control subjects. Among siblings of HIV patients infected through homosexual or heterosexual contact, siblings of HIV/HCV-coinfected patients also had higher mortality than siblings of HIV-monoinfected patients (MRR, 3.09 [95% CI, 1.58–6.04]) and siblings of population control subjects (MRR, 4.58 [95% CI, 2.46–8.52]).

Analyses restricted to Danish-born siblings, youngest siblings, oldest siblings, or siblings of HIV patients without hemophilia did not change the conclusions (table 3). Similarly, results were not affected by adjusting for siblings' birth year or sex (table 3). Among siblings of HIV-infected patients with unknown HCV serostatus (who were excluded from the study), mortality was comparable with that of siblings of HIV-monoinfected patients (MRR, 1.15 [95% CI, 0.59–2.24]). Siblings of HIV-infected patients reporting IDU as their HIV transmission route had increased mortality, relative both to siblings of HIV patients who did not report IDU (MRR, 2.60 [95% CI, 1.67–4.05]) and to control siblings (MRR, 4.19 [95% CI, 2.87–6.11]).

DISCUSSION

We found markedly higher mortality among siblings of patients coinfected with HCV and HIV than among siblings of HIV-monoinfected patients or of population control subjects. This finding implies that factors other than the pathogenicity of HCV infection per se may contribute to high mortality rates among HIV/HCV-coinfected patients. By contrast, siblings of HIV-monoinfected patients had only modestly higher mortality than siblings of population control subjects.

The observed excess risk of death in siblings of HIV/HCV-coinfected individuals may be due to a combination of environmental and genetic factors. It has been well established that adverse socioeconomic conditions during childhood are associated with increased mortality during adulthood because they herald continued lower socioeconomic conditions or through direct effects of childhood environment on later adult health [14, 15]. Thus, one explanation for increased mortality among siblings of HCV-infected patients with HIV may be shared socioeconomic disadvantages. In our study, HCV infection and a history of IDU were strongly associated, and excess mortality in siblings of HIV/HCV-coinfected patients was comparable to

Table 2. Mortality rates for 10-year age intervals.

Age interval	Siblings of HIV/HCV-coinfected patients	Siblings of HIV-monoinfected patients	Siblings of population control subjects
20–29 years	3.4 (2.0–5.7)	1.4 (0.0–2.1)	0.8 (0.8–0.8)
30–39 years	5.2 (3.2–8.5)	1.7 (1.1–2.6)	1.1 (1.1–1.2)
40–49 years	7.3 (3.8–14.0)	1.9 (1.1–3.4)	2.1 (2.0–2.2)

NOTE. Data are deaths/1000 person-years of follow up (95% confidence interval). HCV, hepatitis C virus.

Table 3. Mortality rate ratios (MRRs) in siblings of HIV/hepatitis C virus (HCV)–coinfected patients and HIV-monoinfected patients, compared with siblings of population control subjects.

MMR (95% CI)	Siblings of HIV/HCV-coinfected patients	Siblings of HIV-monoinfected patients
All	4.23 (3.09–5.79)	1.43 (1.10–1.85)
Restricted to subgroups		
Siblings born in Denmark	4.27 (3.11–5.89)	1.44 (1.11–1.86)
Oldest siblings	5.09 (3.58–7.25)	1.47 (1.06–2.04)
Youngest siblings	4.93 (3.30–7.38)	1.33 (0.89–1.97)
Excluding hemophilia	4.45 (3.23–6.12)	1.42 (1.10–1.84)
Sexual HIV transmission	4.58 (2.46–8.52).	1.48 (1.15–1.92)
Adjusted for year of birth	4.20 (3.07–5.76)	1.41 (1.09–1.83)
Adjusted for sex	4.15 (3.03– 5.69)	1.42 (1.10–1.84)

that of siblings of intravenous drug users. Our results could reflect increased mortality associated with a family history of IDU. This, however, does not explain the observed increased mortality among siblings of the subgroup of HIV/HCV-coinfected individuals who had acquired HIV via sexual transmission. Some of these patients may have acquired HIV sexually (or stated heterosexual HIV transmission, to avoid stigmatization) and also have a history of IDU.

There is increasing evidence that genetic factors are associated with alcoholism and drug addiction [16], and a genetic predisposition to substance abuse may have contributed to our findings. Furthermore, Danish studies of adoptees have suggested that genetic factors play a role in the risk of premature all-cause [17–19] and infection-related [19] mortality. Accordingly, HCV infection could be a marker of inherited susceptibility to some infectious pathogens. However, the high parenteral transmissibility of HCV indicates to us that positive HCV serostatus is more likely to be a marker of relevant exposure to HCV than of susceptibility to the infection.

A previous study [20] reported that Danish HIV-infected patients had a risk of death 3–15 times higher than that of the background population. This excess mortality does not seem to be associated with a substantial increased familial risk of death. Thus, the contribution of socioeconomic or genetic factors to mortality in HIV-monoinfected patients appears to have little importance.

In the present population-based cohort study of siblings of HIV-infected individuals, we had complete data on immigration, emigration, and death for Danish residents [21]. The large sample size of the sibling group, together with long and nearly complete follow-up, yielded precise and valid estimates.

A shortcoming of the study was the lack of data on causes of death or HCV serostatus in the siblings. Although shared risk behaviors among HIV/HCV-coinfected patients and their siblings may increase the risk of HCV infection, this factor is not likely to explain more than a fraction of the excess mortality among these siblings. Perinatal or childhood HCV infection occurs infrequently in Denmark, and HCV infection in HIV-negative, otherwise low-risk populations does not increase mortality during the first decades after infection [22–24].

We examined adult mortality and calculated the siblings' observation time from age 20 years until death. Thus, for a large proportion of siblings, the observation time began before HCV and HIV were diagnosed in the index patient. However, because HCV infection in patients with HIV is not a cause of sibling mortality but is most likely a marker of shared inherited or socioeconomic risk factors, this design seems reasonable. Furthermore, any associated potential bias would probably lead to an underestimation of excess mortality.

Because most patients with HIV have their HCV serostatus verified during baseline screening at the first presentation to an HIV clinic, HCV status was not handled as a time-dependent variable. We classified the patients as either HCV infected or not and assumed that most coinfected patients were already infected with HCV at the time of HIV diagnosis [25].

Siblings born outside Denmark were included only if they immigrated to Denmark, which could potentially cause immigration bias. However, few siblings were born outside Denmark, and excluding them from the analysis did not change the study's results. Although registration of sibship was not fully complete in Denmark until 1970, >96% of sibship was recorded from 1959 on, so incompleteness of registration should have introduced only minor bias. Although the number of siblings is related to mortality risk [26] and larger families contributed more to the observation time, the inclusion of only 1 sibling per HIV patient in sensitivity analyses did not affect our findings, regardless of whether the oldest or the youngest sibling was included for each patient. Both HIV-monoinfected patients and HIV/HCV-coinfected patients had fewer siblings than population control subjects. This partly reflects that more HIV patients were born outside Denmark and therefore had no siblings living in Denmark. Among Danish-born individuals, the HIV/HCV-coinfected individuals had fewer siblings than the 2 other groups, possibly because of more broken families, given that we used only full siblings. Because intravenous drug users are extremely marginalized both socially and economically in Denmark [27], our results may not be generalizable to other geographic regions.

In conclusion, the higher mortality observed in siblings of HIV/HCV-coinfected patients suggests that familial factors are involved in HCV-related mortality among HIV patients. Differences in family background and socioeconomic factors may explain part, if not all, of the reported interstudy differences regarding the impact of HCV on mortality among HIV-infected patients. Studies that fail to account for these factors may overestimate the mortality attributable to HCV infection.

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Ischemic Heart Disease in HIV-Infected and HIV-Uninfected Individuals: A Population-Based Cohort Study

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Background. There are concerns about highly active antiretroviral therapy (HAART) causing a progressive increase in the risk of ischemic heart disease. We examined this issue in a nationwide cohort study of patients with human immunodeficiency virus (HIV) infection and a population-based control group.

Methods. We determined the rate of first hospitalization for ischemic heart disease in all Danish patients with HIV infection (3953 patients) from 1 January 1995 through 31 December 2004 and compared this rate with that for 373,856 subjects in a population-based control group. Data on first hospitalization for ischemic heart disease and comorbidity were obtained from the Danish National Hospital Registry for all study participants. We used Cox's regression to compute the hospitalization rate ratio as an estimate of relative risk, adjusting for comorbidity.

Results. Although the difference was not statistically significant, patients with HIV infection who had not initiated HAART were slightly more likely to be hospitalized for the first time with ischemic heart disease than were control subjects (adjusted relative risk, 1.39; 95% confidence interval, 0.81–2.33). After HAART initiation, the risk increase became substantially higher (adjusted relative risk, 2.12; 95% confidence interval, 1.62–2.76), but the relative risk did not further increase in the initial 8 years of HAART.

Conclusions. Compared with the general population, HIV-infected patients receiving HAART have an increased risk of ischemic heart disease, but the relative risk is stable up to 8 years after treatment initiation.

Concerns have been raised that HIV-infected patients treated with HAART have a progressively increasing risk of ischemic heart disease because of dyslipidemia induced by the therapy [1, 2]. Two studies have examined the impact of HAART on intima media thickness, measured by ultrasonography, as a marker for ischemic heart disease, with inconsistent findings [3, 4]. Cohort studies of ischemic heart disease in HIV-infected patients also have had conflicting results [5–11]. The limitations of these studies included the use of different data sources to ascertain cases of ischemic heart disease in the patients with HIV infection and in the control group or the absence of control subjects from the general population. The latter may be of particular importance, because the diagnosis of ischemic heart disease has evolved during the study periods. To overcome these methodological shortcomings, we conducted a cohort study of ischemic heart disease in Danish patients with HIV infection and control subjects from the general population using 3 nationwide registries: the Danish HIV Cohort Study, the Danish Civil Registration System, and the Danish National Hospital Registry [12–14]. The study was designed to examine whether HIV-infected patients receiving HAART have an elevated relative risk of a first hospitalization for ischemic heart disease, compared with the general population. If that prediction proved to be correct, the study further aimed to establish whether this disparity in relative risk increased with duration of HAART.

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METHODS

Setting

As of 1 January 2005, Denmark had a population of 5,400,000; the estimated prevalence of HIV infection in the adult population is 0.07% [13]. Denmark's tax-funded health care system provides antiretroviral treatment free of charge to all HIV-positive residents. Treatment of HIV infection is provided in only 8 specialized medical centers, where patients are seen on an outpatient basis at intended intervals of 12 weeks. During our study period, national criteria for HAART initiation were presence of an HIV-related disease, acute HIV infection, pregnancy, $CD4^+$ cell count <300 cells/μL, and, until 2001, a plasma HIV RNA load >100,000 copies/mL. Structured treatment interruptions have generally not been recommended in Denmark.

Study Population and Data Collection

HIV cohort. The Danish HIV Cohort Study, which has been described elsewhere, includes all HIV-infected patients treated in the 8 specialized centers in Denmark from 1 January 1995 through 31 December 2004 [13]. The cohort includes 4252 Danish residents (as recorded in the Danish Civil Registration System) who received a diagnosis of HIV infection before 1 January 2005 and were >16 years of age at the time of diagnosis.

In our study, the index date was defined as the HIV infection diagnosis date for all cohort members except those who received a diagnosis before 1 January 1995; for the latter patients, the index date was set at 1 January 1995. The study included all 3953 Danish patients who (1) lived in Denmark on the index date and (2) were not hospitalized with ischemic heart disease prior to this date. HAART was defined as a treatment regimen of at least 3 antiretroviral drugs that included a nonnucleoside reverse-transcriptase inhibitor, a protease inhibitor, and/or abacavir, or a treatment regimen with a combination of a nonnucleoside reverse-transcriptase inhibitor and a boosted protease inhibitor.

General population control cohort. The Danish Civil Registration System, which has stored information on all Danish residents since 1968, was used to identify control subjects from the general population for the study [12]. For each person, it records a 10-digit unique identification number, date of birth, sex, residence location, dates of immigration or emigration, and date of death. We aimed to identify 99 control subjects for each HIV-infected patient, matched by sex, age (month and year of birth), and municipality of residence. Because of the shortage of eligible control subjects in some municipalities, we identified 94.5 control subjects per patient with HIV infection (a total of 373,856 control subjects). We also extracted data on death and emigration for patients with HIV infection and the control subjects from the Danish Civil Registration System.

Hospitalization with Ischemic Heart Disease and Comorbidities

Hospitalization data for all study subjects were obtained from the Danish National Hospital Registry, established in 1977 [14]. This registry contains records of all discharge diagnoses (coded according to the International Classification of Diseases, 8th revision, until the end of 1993, and the International Classification of Diseases, 10th revision, codes thereafter) and procedure codes for patients treated in Danish hospitals. We defined the study outcome, "the first hospitalization for verified ischemic heart disease," as a first-time discharge diagnosis of myocardial infarction (codes 410.09 or 410.99 in International Classification of Diseases, 8th revision; codes I21.0 to I21.9 in International Classification of Diseases, 10th revision) or a first-time coronary artery bypass and percutaneous coronary intervention (procedure codes KFNA00 to KNFG96). From the Danish National Hospital Registry, we also extracted data on angina pectoris, sudden death from heart disease, heart diseases other than the study outcome, and comorbidities known to be risk factors for ischemic heart disease (diabetes, alcoholism, hypertension, liver disease, and kidney disease).

Statistical Analysis

We constructed Kaplan Meier curves for time until first hospitalization for ischemic heart disease according to HAART status. Follow-up ceased on the earliest of the following events: date of death, emigration, loss to follow-up, first hospitalization with ischemic heart disease, or 1 January 2005. The period from the index date until HAART initiation or end of follow-up, whichever came first, was considered to be the non-HAART period. The time following HAART initiation was considered the HAART period, even if treatment interruptions occurred.

We used stratified Cox's regression to compute rate ratios of the first hospitalization with ischemic heart disease as estimates of relative risk. We assessed the proportional hazards assumption with plots and tests that were based on smoothed scaled Schoenfeld residuals. Each comorbidity diagnosis was included in the regression model as a design variable. Separate analyses were performed for the non-HAART and HAART periods. For the HAART period, subanalyses were performed for 2 time intervals: $\leqslant$90 days of HAART and >90 days of HAART. We also computed rates of first hospitalization with ischemic heart disease for 2-year periods and up to 8 years after HAART initiation.

Because accuracy of coding may differ by discharge diagnosis, we performed several sensitivity analyses to examine how changes in definition affected the findings. In one analysis, we included angina pectoris and sudden cardiac death in the definition of first hospitalization for verified ischemic heart disease. In another analysis, we defined the outcome as only the first-time discharge diagnosis of myocardial infarction.

Data analysis was performed using SPSS software, version

Table 1. Characteristics of HIV-infected patients and control subjects.

Variable	HIV-infected patients (n = 3953)	Control subjects (n = 373,856)
Duration of follow-up in the non-HAART period, person-years	9271	1,272,956
Duration of follow-up in the HAART period, person-years	13,593	1,389,722
Duration of follow-up in the non-HAART period, median years (IQR)	1.67 (0.37–3.09)	2.13 (0.58–5.20)
Duration of follow-up in the HAART period, median years (IQR)	5.23 (2.56–7.55)	5.95 (3.25–7.79)
Death during follow-up	968 (24.5)	12,084 (3.2)
Emigration during follow-up	107 (2.7)	10,186 (2.7)
Lost to follow-up	14 (0.4)	1304 (0.3)
Age at index date, median years (IQR)	36.8 (30.8–44.6)	36.4 (30.6–44.0)
Male sex	3037 (76.8)	285,087 (76.3)
Infection risk factor		
MSM	1835 (46.4)	…
Heterosexual sex	1364 (34.5)	…
Injection drug use	491 (12.4)	…
Other/unknown	263 (6.7)	…
White race	3258 (82.4)	…
Received diagnosis of HIV infection before 1 January 1995	1912 (48.4)	…
First hospitalization for ischemic heart disease		
After the index date and before HAART initiation		
No. of subjects	14	1946
No. (%) of subjects with myocardial infarction as the outcome-defining event	11/14 (78.6)	1461/1946 (75.1)
After HAART initiation		
No. of subjects	57	2817
No. (%) of subjects with acute myocardial infarction as the outcome-defining event	44/57 (77.2)	1973/2817 (70.0)
During the first 90 days after HAART initiation		
No. of subjects	7	82
No. (%) of subjects with acute myocardial infarction as the outcome-defining event	4/7 (57.1)	63/82 (76.8)
Initiated HAART during study period with no hospitalization for ischemic heart disease before HAART initiation	2765	…
Age at start of HAART, median years (IQR)	38.9 (33.0–46.4)	…
Time from diagnosis of HIV infection to HAART initiation, median years (IQR)	3.2 (0.2–8.2)	…
HIV load at HAART initiation, median $\log^{10}$ copies/mL (IQR)	4.9 (4.2–5.4)	…
$CD4^+$ cell count at HAART initiation, median cells/μL (IQR)	182 (74–290)	…
Antiretroviral naive at HAART initiation	1804 (65.2)[a]	…
NRTI in initial HAART regimen	2738 (99.0)[a]	…
NNRTI in initial HAART regimen	857 (31.0)[a]	…
Protease inhibitor in initial HAART regimen	1923 (69.5)[a]	…
Ever exposed to NRTI in HAART	2743 (99.2)[a]	…
Ever exposed to NNRTI in HAART	1963 (71.0)[a]	…
Ever exposed to protease inhibitor in HAART	2080 (75.2)[a]	…

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Index date, date of diagnosis of HIV infection (if diagnosed before 1995, index date is 1 January 1995). IQR, interquartile range; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

[a] Percentage of patients who initiated HAART during the study period with no hospitalization for ischemic heart disease prior to HAART initiation.

12.0 (Norusis; SPSS), and R Development Core Team software (R Foundation for Statistical Computing). The study was approved by the Danish Data Protection Agency.

RESULTS

The study cohort included 3953 HIV-infected patients and 373,856 control subjects (table 1). Patients and control subjects were well-matched in terms of age at index date, sex, emigration, and loss to follow-up. During the non-HAART period, the risk of first hospitalization for ischemic heart disease was slightly higher in patients with HIV infection than in control subjects (adjusted relative risk, 1.39; 95% CI, 0.82–2.36) (figure 1 and table 2). During the HAART period, the risk increase was substantially higher (adjusted relative risk, 2.12; 95% CI,

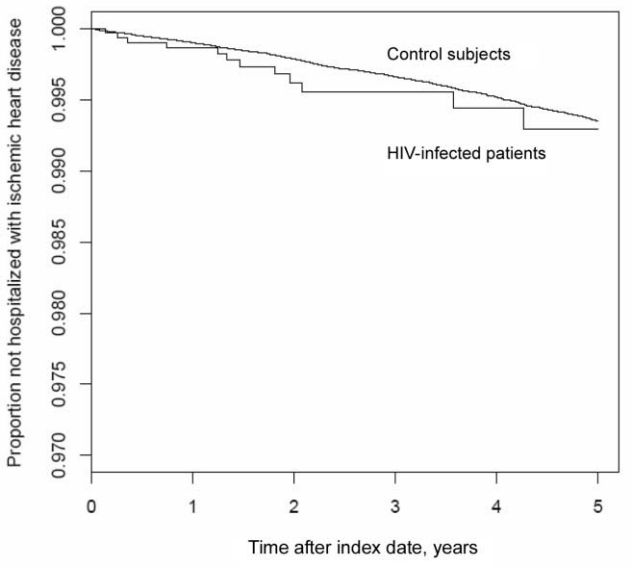

Figure 1. Kaplan Meier curves for time from index date to first verified hospitalization with ischemic heart disease in HIV-infected patients in the non-HAART period and control subjects.

1.62 to 2.76) (figure 2 and table 2). Examination of the smoothed scaled Schoenfeld residuals indicated a higher relative risk of first hospitalization for ischemic heart disease in the first 90 days after HAART initiation (data not shown). In a separate analysis of this time period, the adjusted relative risk for a first ischemic heart disease hospitalization was 7.44 (95% CI, 3.35–16.5). This is considerably higher than during the rest of the HAART period, for which the adjusted relative risk was 1.92 (95% CI, 1.45–2.55) (table 2).

Within the 2-year intervals following HAART initiation, the rates of first hospitalization for ischemic heart disease increased in the HIV-infected individuals (0–2-year period, 3.82 cases per 1000 person-years of observation [PYR] [95% CI, 2.44–5.99 cases per 1000 PYR]; 6–8-year period, 6.51 cases per 1000 PYR [95% CI, 3.50–12.1 cases per 1000 PYR]). However, compared with the control subjects, the relative risk for patients treated with HAART did not increase during the 8-year period after HAART initiation (figure 3). From the period 1995–1998 to the period 2002–2004, the incidence of first hospitalization for ischemic heart disease in control subjects increased from 1.3 cases per 1000 PYR to 2.3 cases per 1000 PYR, and in the same interval, the median age of control subjects increased from 38.8 years to 41.2 years. These 2 parameters increased in the HAART-exposed population, as well (table 3).

Among patients with a $CD4^+$ cell count >200 cells/μL at HAART initiation, relative risk, compared with control subjects, was 1.80 (95% CI, 1.17–2.78), and among patients with a $CD4^+$ cell count $\leq$200 cells/μL, relative risk was 2.28 (95% CI, 1.63–3.19). Patients initiating HAART with a viral load of $\leq 10^5$ HIV RNA copies/mL had a relative risk of ischemic heart disease of 1.52 (95% CI, 0.98–2.37), compared with a relative risk of 2.52 (95% CI, 1.69–3.78) among patients with a viral load $>10^5$ HIV RNA copies/mL. For patients initiating HAART within 1 year after receiving a diagnosis of HIV infection, relative risk of ischemic heart disease was 2.38 (95% CI, 1.56–3.64), and among patients whose HAART treatment was delayed longer than 1 year following receipt of a diagnosis of HIV infection, relative risk was 1.90 (95% CI, 1.36–2.65). During the 30 days after the first hospitalization for ischemic heart disease, 5 (8.8%) of the patients with HIV infection died, compared with 107 (3.8%) of the control subjects.

When first hospitalization for ischemic heart disease was defined only as a discharge diagnosis of myocardial infarction, the relative risk estimate remained unchanged; for the non-HAART period, the relative risk was 1.37 (95% CI, 0.75–2.48), and for the HAART period, the relative risk was 2.29 (95% CI, 1.69–3.09). Including angina pectoris and sudden cardiac death in the definition of the first hospitalization for ischemic heart disease also had little impact on relative risk estimates; for the non-HAART period, the relative risk was 1.47 (95% CI, 0.88–2.45), and for the HAART period, the relative risk was 2.05 (95% CI, 1.57–2.67). Excluding nonwhite individuals from the analysis had almost no effect on the estimates; for the non-HAART period, the relative risk was 1.34 (95% CI, 0.77–2.32), and for the HAART period, the relative risk was 1.99 (95% CI, 1.51–2.62).

DISCUSSION

We found that, after initiation of HAART, the risk of ischemic heart disease was higher among HIV-infected patients than

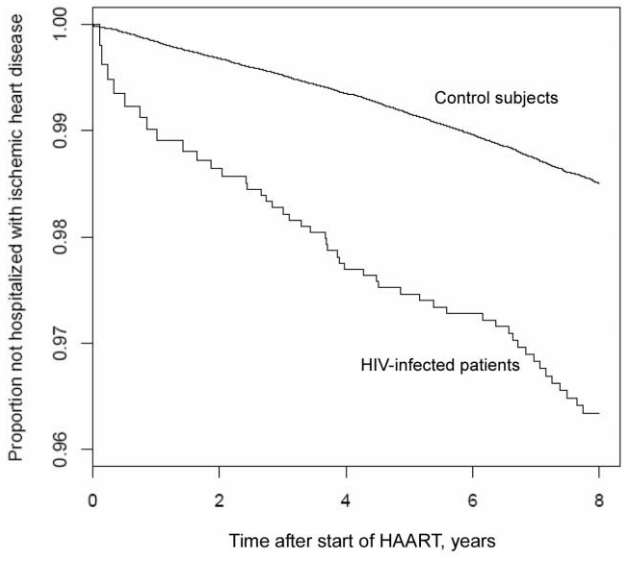

Figure 2. Kaplan Meier curves for time from HAART initiation to first verified hospitalization with ischemic heart disease in HIV-infected patients and control subjects.

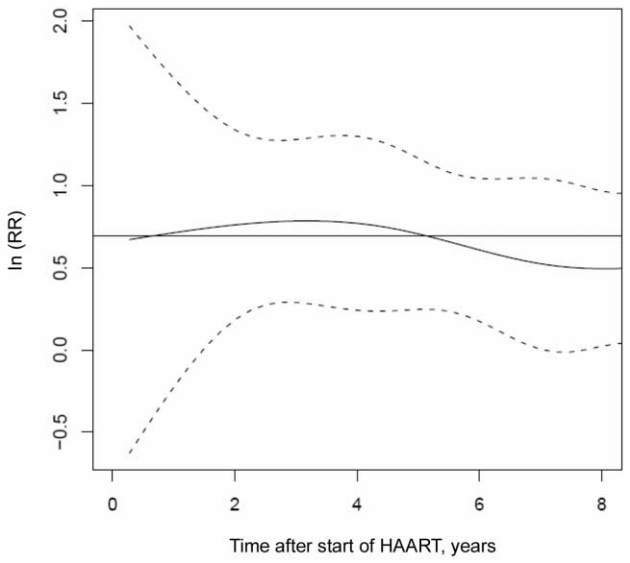

Figure 3. Plot of smoothed scaled Schoenfeld residuals of relative risk (RR) of first hospitalization for ischemic heart disease after HAART initiation. The horizontal configuration of the plot indicates that no increase in RR of first hospitalization occurs during the first 8 years after HAART initiation. RR of $2(ln(2) = 0.693)$ is indicated by the solid straight line. The first 90 days after HAART initiation were excluded from analysis. 95% CIs are indicated by the broken lines. ln, natural log.

among control subjects. However, we observed no progressive increase in the relative risk in the 8-year period following HAART initiation.

In this study, we used a truly population-based control cohort and were able to achieve a longer follow-up period than that achieved by earlier studies. Comparison with a population-based control group allowed us to account for potential bias introduced from differences in age and calendar time. Importantly, we used the same source of data to ascertain outcome for all study subjects. We are aware of no other study with a similar design addressing the important question of HAART-related cardiac events.

We relied on registry-based discharge diagnoses to ascertain the almost 5000 outcome events in this study. Although discharge diagnoses in general may not be entirely accurate, the registration of myocardial infarction, coronary bypass surgery, and percutaneous coronary intervention have been shown to be highly valid [14, 15]. Because the clinical criteria for myocardial infarction and indications for invasive procedures were revised during the study period [16], the increase in risk of first hospitalization for ischemic heart disease likely reflects the increase in age among the study population and changes in diagnostic and treatment practices related to ischemic heart disease. Although we missed patients who died before hospitalization for ischemic heart disease, we assume that rates of prehospitalization death from this cause are not likely to differ between patients and control subjects. Therefore, potential underreporting of ischemic heart disease culminating in death before hospitalization did not bias our relative risk estimates.

An important study limitation is lack of data on certain risk factors for ischemic heart disease, such as smoking, which is presumed to be more frequent among HIV-infected patients than among the general population [17]. Failure to account for smoking may have led us to overestimate the relative risk of ischemic heart disease associated with HAART. Also, we cannot exclude the possibility that the general population receives more-optimal treatment for potential risk factors for ischemic heart disease. However, we find it unlikely that major changes in general risk-factor profiles occurred suddenly at the time of HAART initiation. We therefore expect that estimates of changes in relative risk over time are robust.

In contrast to our study, the Data Collection on Adverse Events of Anti-HIV Drugs (D.A.D.) study reported that HAART caused a progressive increase in the risk of ischemic heart disease, with relative risk increasing by 26% for each year of HAART [7]. The study used a prospective cohort design, but it did not include follow-up of all patients from the time of HAART initiation, had a shorter follow-up period, and did not include an HIV-negative control population. The latter may be crucial, because we observed a substantial increase over calendar time in the frequency of first hospitalization with ischemic heart disease in the control subjects, as well as in the HIV-infected population (table 3). In recent years clinicians have focused on the risk of ischemic heart disease, and increased guidance from blood lipid tests has expanded the use of statins and antiretroviral regimens with more-favorable lipid profiles. These changes in treatment strategies may potentially diminish

Table 2. Relative risk (RR) for first hospitalization for ischemic heart disease in patients with HIV infection, compared with control subjects, by treatment period.

Period	Crude RR (95% CI)	Adjusted RR (95% CI)
Non-HAART period	1.38 (0.81–2.33)	1.39 (0.82–2.36)
HAART period	2.06 (1.58–2.68)	2.12 (1.63–2.76)
HAART period including only the initial 90 days after HAART initiation	6.70 (3.07–14.6)	7.44 (3.35–16.5)
HAART period excluding the first 90 days after HAART initiation	1.88 (1.42–2.49)	1.92 (1.45–2.55)

Table 3. Incidence rate (IR) of first hospitalization for ischemic heart disease after HAART initiation, stratified by year.

Period	Age at start of period, median years		IR[a] (95% CI)	
	Patients with HIV infection	Control subjects	Patients with HIV infection	Control subjects
1995–1998	38.9	38.8	3.1 (1.6–6.0)	1.3 (1.2–1.4)
1999–2001	39.7	39.6	3.8 (2.4–6.0)	1.8 (1.7–1.9)
2002–2004	41.4	41.2	4.6 (3.2–6.6)	2.4 (2.3–2.5)

[a] IR was defined as number of hopitalizations per 1000 person-years of observation.

a putative increase in the relative risk of ischemic heart disease. However, the D.A.D. study found that the risk profile for ischemic heart disease has worsened over time [18]. In our study, blood lipids were not measured systematically among patients with HIV infection, and we did not have access to data on the lipid profiles of the control subjects. Although blood lipids are likely to be on the causal pathway, absence of information prohibited us from estimating any potential residual effect of HAART.

The sudden increase in the risk of ischemic heart disease after HAART initiation, observed both in our study and in the D.A.D. study, parallels findings of increased cholesterol and triglyceride blood levels in a number of other studies [19, 20]. However, the magnitude and the timing of the changes indicate that other factors are also involved in the disease process. A more gradual increase in the risk would be expected if lipid accumulation in the atherosclerotic plaques were the main risk factor for ischemic heart disease after HAART initiation. Other mechanisms, such as inflammation or changes in platelet or endothelial function, must be considered as potential explanations for the sudden expansion and instability of the atherosclerotic plaques. It is noteworthy that, during the initial months after HAART initiation, an ill-defined syndrome of paradoxical immune reconstitution occurs in some patients as a response to opportunistic pathogens [21]. This syndrome is associated with low nadir $CD4^+$ cell counts and rapid increase in $CD4^+$ cell counts [22, 23].

We observed a higher risk of first ischemic heart disease hospitalization during the initial months after HAART initiation and found a larger relative risk among patients who initiated HAART with a higher viral load and lower $CD4^+$ cell count, suggesting that immune reconstitution may partly explain the excess risk after HAART initiation. However, we cannot rule out the possibility that the association between HAART initiation and excess risk of first hospitalization with ischemic heart disease is caused partly by a measurement bias: patients with HIV infection have more frequent contacts with the health care system and, therefore, are more likely to have ischemic heart disease detected than are members of the general population [24]. Given the abrupt increase in the risk of ischemic heart disease following HAART initiation, body composition changes and derived metabolic changes are unlikely to be causal factors in this process, because these changes usually occur after years of antiretroviral therapy. Partly in accordance with our observations, the Strategies for Management of Antiretroviral Therapy study found that starting and stopping HAART might be related to an increased risk of cardiovascular incidents [25].

In conclusion, we observed an increased risk of ischemic heart disease in HIV-infected patients immediately after HAART initiation. The risk increase was moderate and of the same order as that introduced by smoking 1–4 cigarettes per day [26], and it was less than that observed in patients with insulin-dependent diabetes [27]. We found no evidence of an increase in the relative risk over time, which suggests that HAART does not have an aggressive atherogenic effect. The pathogenetic basis for the increase needs to be clarified to optimize prophylaxis. Furthermore, it should be established whether risk of ischemic heart disease is linked to specific drug classes, as a recent study has suggested [28].

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Improved survival in HIV-infected persons: consequences and perspectives

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A human immunodeficiency virus (HIV) patient in 2007 has the option to commence an antiretroviral regimen that is extremely efficacious in suppressing the virus and has few side effects. In a recent study, we estimated the median remaining lifetime of a newly diagnosed 25-year-old HIV-infected individual to be 39 years. The prospect of a near-normal life expectancy has implications for the HIV-infected persons as well as for the handling of the disease in the healthcare system. The patients can now on a long-term perspective plan their professional career, join a pension plan and start a family. Further, they may expect to be treated equally with other members of society with respect to access to mortgage, health insurance and life insurance. As the infected population ages, more patients will contract age-related diseases, and the disease burden on some individuals may even come to be dominated by non-HIV-related conditions that may have a worse prognosis and therefore become more important than HIV-related conditions. Despite the improvements in antiretroviral therapy, there is still an excess mortality among HIV patients, which appears to be only partially attributable to immunodeficiency, with lifestyle factors potentially playing a pronounced role. Consequently, an effort to further increase survival must target risk factors for both HIV-related and -unrelated mortality. The continuation of the positive trend may be achieved by increased HIV testing, earlier initiation of antiretroviral therapy, improved drug adherence, prevention and treatment of HIV-unrelated co-morbidity and collaboration with other medical specialists to treat an ageing co-morbidity-acquiring HIV population.

Keywords: prognosis, treatment strategies, co-morbidity, mortality

Background

The effectiveness of highly active antiretroviral therapy (HAART) against the human immunodeficiency virus (HIV) has been a medical success story. For those fortunate enough to have access to HAART, an inevitably deadly disease has turned into a chronic condition. In the 1980s, simply finding a drug or drug combination that could delay AIDS or death was the main clinical goal. In the mid-1990s, triple-combination therapy was introduced, leading to substantially prolonged survival. Simultaneously, it was shown that the substrate for the clinical effectiveness was suppression of HIV replication.[1] Many patients experienced the comfort of a rising CD4 cell count and reversal of their AIDS-defining conditions. However, short-term and long-term side effects of the drugs became increasingly concerning, whereas episodes of virological failure led to the development of drug resistance, forcing patients to resort to often less efficacious second- or third-line regimens. Pharmaceutical companies began competing to develop new drugs with fewer side effects, lower pill burden and a better tolerance to non-compliance. Patients and physicians speculated whether controlled treatment interruptions could bring about a clinical success by delaying the potential exhaustion of available drug combinations and reducing the harm due to side effects. The intensive drug development and the massive research into mechanisms of resistance and side effects have paid off. An HIV patient in 2007 has the option to commence a drug combination that is both efficacious in suppressing the virus and has few side effects. Despite HIV's ability to escape antiviral pressure, the rate of resistance to the antiviral drugs—a major problem in the early years when the regimens were suboptimal—is declining in a number of settings and may be $<1\%$ annually. Thus, there is growing optimism among HIV experts

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that a large proportion of their patients will be able to remain on their initial regimens and survive for many years. The big question has been, though, *how long*?

Survival of HIV-infected persons

Our group has addressed this question in the Danish HIV Cohort Study, using data from a population-based cohort of all HIV-infected persons in Denmark, a country with free tax-supported medical care, including universal, income-independent access to HAART.[2] The high quality of the Danish Civil Registration System[3] enabled us to compare, with little attrition, the survival of HIV patients with that of a matched cohort from the general population. Life-table methods were used to estimate survival of a 25-year-old HIV-infected person, regardless of whether the person had started HAART. The estimated median remaining lifetime has increased from 8 years in 1995–96 to 23 years in 1997–99 to 33 years in 2000–05. Among persons not co-infected with the hepatitis C virus (HCV), the median remaining lifetime in 2000–05 was 39 years (95% CI: 35–40 years), similar to that of a young person with diabetes.[4] In comparison, the median remaining lifetime for a 25-year-old HIV-uninfected person was 51 years. Furthermore, we found that neither time since diagnosis nor duration of HAART was associated with an increased mortality. Importantly, the highest mortality was observed in the first year after the initiation of treatment.

Immediate implications of the improved prognosis

As clinicians know, the prognosis for individual HIV patients depends on many determinants, including immune status at the time of diagnosis, harbouring of a drug-resistant virus strain, adherence to treatment and concomitant infection with HCV. Nevertheless, the overall improved prognosis, with the prospect of a near-normal life, has implications for the HIV-infected persons as well as for their physicians. The patients may now plan their professional career, join a pension plan, start a family—things that just a few years ago seemed to be irrelevant luxuries. They may expect to be treated equally with other members of society and to have easy access to mortgage, health insurance and life insurance. They also expect to receive high-quality healthcare for non-HIV-related conditions, including fertility treatment. As the patients now get older, they will contract age-related diseases, and the disease burden on some individuals may even come to be dominated by non-HIV-related conditions. Some of these diseases may have a worse prognosis and therefore become more important than HIV for some patients. It would be important to know when an HIV-infected person needs a hip replacement, a bypass operation or even a cardiac transplantation.[5] Elements of healthy lifestyle—smoking cessation, weight loss and regular physical exercise—that take 10 years or more to yield full benefits are becoming increasingly relevant for HIV patients. Furthermore, they should be offered prophylactic treatments, such as cholesterol-lowering therapy and antihypertensive treatment, just as their non-HIV-infected counterparts do.

Why do HIV patients still have a higher risk of death?

Even though survival has increased markedly, HIV-infected persons still die at rates that are 3–15 times higher than the general population.[2] Cause-specific rates have decreased for both HIV-related and non-HIV-related mortality, but the decreased risk of AIDS has led to a change in patterns of co-morbidity and causes of death, and most deaths (50% to 70% of all deaths) are now non-HIV-related.[2,6–8]

Common causes of non-HIV-related death are non-AIDS-defining cancers (~10% of all deaths), cardiovascular diseases (~7%), substance abuse-related death (~7%), liver-related death (up to 15% reported) and bacterial infections (~6%).[7–9] The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study found mortality rates of non-AIDS-defining cancers to be related to the degree of immunodeficiency. Some cancers are known to be associated with lifestyle-related viral infections, such as hepatitis B virus (hepatocellular carcinoma), HCV (hepatocellular carcinoma and lymphoma) or human papilloma virus (anal, mouth and throat cancer),[9] whereas others may be associated with smoking (cancer of lung, mouth and throat).[10] Liver-related deaths are mainly seen in hepatitis C or B co-infected patients and the actual risk varies with the prevalence of these co-infections.[11] We have found that a large part of the increased mortality seen in HIV/HCV co-infected individuals is associated with family-related risk behaviours—mainly drug abuse—and to a lesser extent, with the HCV infection itself.[12] Behavioural risk factors for disease and death, such as cigarette smoking and excessive alcohol consumption, are common in many HIV-infected populations.[13,14] Thus, the excess mortality among HIV patients appears to be only partially attributable to immunodeficiency, with lifestyle factors potentially playing a pronounced role. Consequently, an effort to further reduce mortality and increase survival must target risk factors for both HIV-related and HIV-unrelated mortality.

How can we provide better care for the patients?

A reduction in HIV-related mortality requires improved virological suppression, and research has shown that adherence to therapy is the key to success.[15] The first step is easy and free access to drugs and healthcare, which should be supplemented by a coordinated effort of experienced care teams—physicians, nurses and social workers—in order to adequately address each individual's needs, problems and taboos. Further, and in line with current CDC recommendations,[16] test frequency must be increased for individuals at risk of being HIV-infected, including all adults in healthcare settings. This may help identify HIV-infected patients at an earlier stage of the disease and thereby enable timely therapy initiation. Reducing non-HIV-related mortality calls for a multifaceted approach whose success partly depends on behavioural changes that physicians can merely encourage, but not enforce. In addition, physicians must be aware that the HIV-infected population is getting older and therefore becomes increasingly affected by the diseases common in the general population. Optimal treatment and prevention therefore require the expertise of other medical specialists.

What can be done to stem the epidemic?

In order to optimize the benefit of the highly efficacious antiretroviral drugs that are available today, we must understand how the new treatment strategies may affect the spread of the disease on the population level. The improved survival increases the prevalence of persons who carry HIV and are thus at risk for

transmitting the virus to others. In addition, the awareness of improved prognosis may cause people to be less afraid of getting infected and cause them to become less vigilant. Furthermore, increased use of HAART may lead to resurgence of drug resistance. In contrast, a combination of high adherence and efficacious regimens will maintain viral suppression in the population and prevent the development of resistance. In support of the optimistic view, a recent population-based study from our group showed an increase in viral suppression and a decreasing incidence of potential resistance.[17] Finally, there are persons who are unaware of their HIV infection; most of them have high viral loads and are more likely to engage in high-risk behaviours than they would if they were aware of being infected. The prevalence of these persons is unknown, and thus the extent of the problem is difficult to estimate.

Hence, the following needs to be considered. First, controlled treatment interruptions have been shown to do more harm than good in the individual,[18] nor are they justifiable from a population perspective, because of the increased risk of transmission during periods of interruption. Secondly, initiating HAART at an earlier stage—possibly treating all patients—is an intervention that may restrain the spread of the epidemic. Thirdly, intensified testing will help reduce the prevalence of risk behaviours and improve viral suppression on the population level.

Other research questions are pending: What is the long-term impact of HIV and HAART on the risk of non-HIV diseases? How do antiretroviral drugs interact with other drugs in older individuals? Can we tailor individual regimens based on genetic markers for drug susceptibility and on individual risks for adverse drug reactions? What are the social and economic consequences of a growing population of HIV-infected persons? Some will require intensive medical care and receive financial support from the state, but many will contribute to the economy through work and tax payments. Ultimately, how can we transfer the success in the Western world to resource-poor settings, where poverty may force patients into antiretroviral drug-sharing and treatment interruptions? A requisite, contributory step forward will be the development of a preventive and/or therapeutic HIV vaccine.[19]

Conclusion

Many HIV-infected persons with access to antiretroviral therapy have a near-normal life expectancy, but mortality among them is still higher than that in the general population. The continuation of the positive trend may be achieved by vaccine development, increased HIV testing, earlier HAART initiation, individually tailored regimens, improved drug adherence, prevention and treatment of HIV-unrelated co-morbidity and collaboration with other medical specialists to treat an ageing co-morbidity-acquiring HIV population.

Transparency declarations

None to declare.

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Cause-Specific Excess Mortality in Siblings of Patients Co-Infected with HIV and Hepatitis C Virus

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Background. **Co-infection with hepatitis C in HIV-infected individuals is associated with 3- to 4-fold higher mortality among these patients' siblings, compared with siblings of mono-infected HIV-patients or population controls. This indicates that risk factors shared by family members partially account for the excess mortality of HIV/HCV-co-infected patients. We aimed to explore the causes of death contributing to the excess sibling mortality.** ***Methodology and Principal Findings.*** **We retrieved causes of death from the Danish National Registry of Deaths and estimated cause-specific excess mortality rates (EMR) for siblings of HIV/HCV-co-infected individuals (n = 436) and siblings of HIV mono-infected individuals (n = 1837) compared with siblings of population controls (n = 281,221). Siblings of HIV/HCV-co-infected individuals had an all-cause EMR of 3.03 (95% CI, 1.56–4.50) per 1,000 person-years, compared with siblings of matched population controls. Substance abuse-related deaths contributed most to the elevated mortality among siblings [EMR = 2.25 (1.09–3.40)] followed by unnatural deaths [EMR = 0.67 (−0.05–1.39)]. No siblings of HIV/HCV co-infected patients had a liver-related diagnosis as underlying cause of death. Siblings of HIV-mono-infected individuals had an all-cause EMR of 0.60 (0.16–1.05) compared with siblings of controls. This modest excess mortality was due to deaths from an unknown cause [EMR = 0.28 (0.07–0.48)], deaths from substance abuse [EMR = 0.19 (−0.04–0.43)], and unnatural deaths [EMR = 0.18 (−0.06–0.42)].** ***Conclusions.*** **HCV co-infection among HIV-infected patients was a strong marker for family-related mortality due to substance abuse and other unnatural causes. To reduce morbidity and mortality in HIV/HCV-co-infected patients, the advances in antiviral treatment of HCV should be accompanied by continued focus on interventions targeted at substance abuse-related risk factors.**

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INTRODUCTION

Co-infection with HCV is a marker for poor prognosis in HIV-infected individuals. It is unclear whether the prognostic impact is caused directly by the viral disease, or whether it is an epiphenomenon of the infection [1–3]. It has been suggested that HCV exerts a direct pathogenic effect by compromising the immune restoration induced by highly active antiretroviral therapy (HAART) [1,4,5], but it has been difficult to separate the direct pathogenic effects of HCV from indirect effects of associated risk factors. In most settings, HCV infection is closely linked with intravenous drug use (IDU), which is associated with risk factors such as mental health illnesses, depression and alcohol abuse [6,7].

In a recent attempt to uncover the impact of the indirect effects, we examined the mortality in siblings of HIV/HCV-co-infected individuals. We found three- to four-fold higher mortality among siblings of HCV/HIV-co-infected patients, compared to siblings of HIV-mono-infected individuals and siblings of population controls [8]. This indicates that risk factors shared by family members partially account for the excess mortality of HIV/HCV-co-infected patients. Given the high parenteral transmissibility of HCV, we hypothesized that HCV infection is a marker of high-risk lifestyle associated with intravenous drug use (IDU). However, the excess mortality could also be mediated through shared susceptibility to some infectious pathogens or increased prevalence of HCV infection among siblings of HIV/HCV-co-infected individuals.

To explore the excess mortality shared among family members, we used a nationwide population-based Danish cohort to compare cause-specific mortality rates, including mortality associated with drug and alcohol abuse, among three groups: siblings of HIV/HCV-co-infected individuals, siblings of HIV-mono-infected individuals, and siblings of general population controls.

METHODS

The study setting and methods used to identify siblings have been described in detail previously [8]. Briefly, we used the population-based Danish HIV Cohort Study (DHCS) [9] to identify all Danish HIV mono-infected and HIV/HCV co-infected patients

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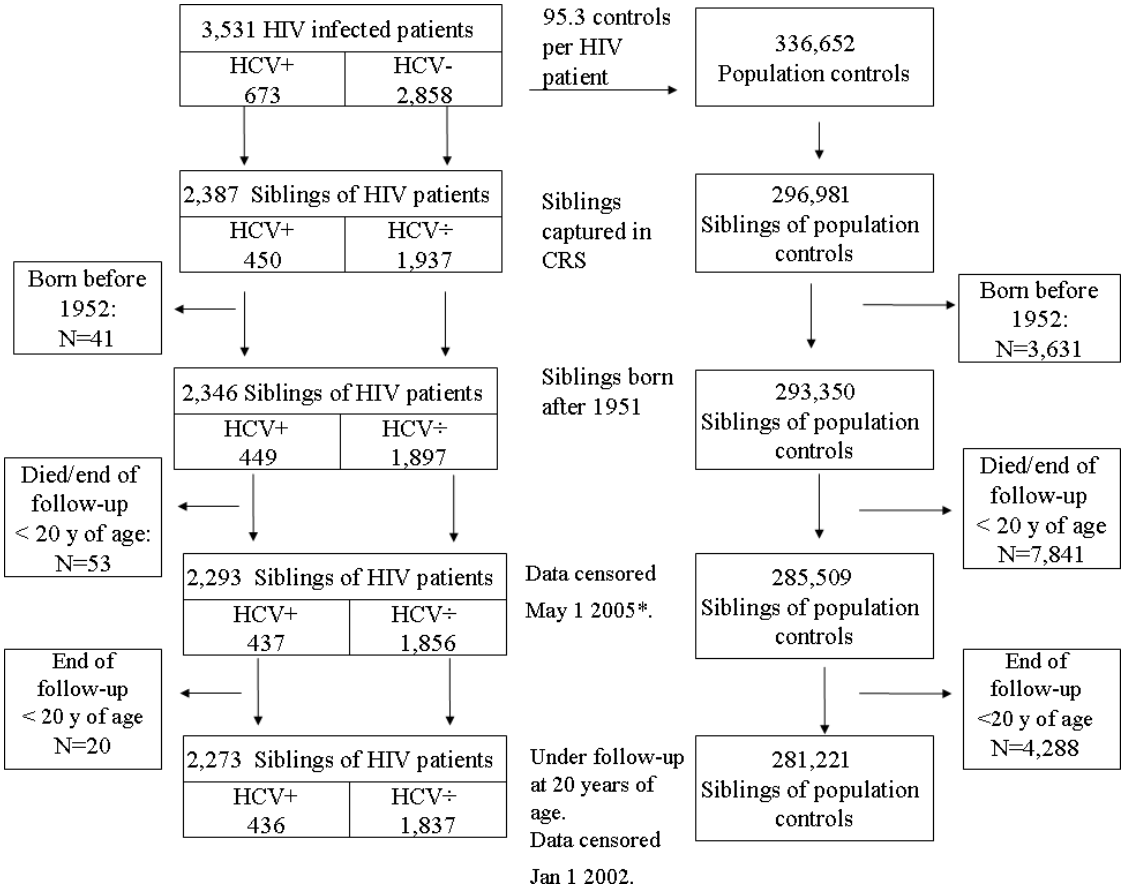

Figure 1. Summary of the study design. CRS, the Danish Civil Registration System; HCV, Hepatitis C virus. * Number of siblings in [8]
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treated in Danish HIV Centres since 1995. HIV treatment in Denmark is restricted to eight specialised centres, and the Danish health care system provides free tax-supported medical care, including antiretroviral treatment for HIV.

We identified up to 99 population controls per patient, matched by gender, age and residency from the Danish Civil Registration System (CRS). CRS is an electronic database established in 1968, which tracks vital status, migration, residency and kinship for all Danish inhabitants [10]. CRS records contain a unique 10-digit civil registration number that allows accurate record linkage with other registries. For both HIV-infected patients and population controls, we identified all full siblings born after 1951 (as registration of kinship was incomplete before this date) and obtained their dates of death or emigration from CRS. Based on the HIV patients' HCV serostatus or tests for HCV-RNA, siblings of HIV-infected individuals were classified as siblings of HIV-mono-infected individuals or siblings of HIV/HCV-co-infected individuals [8]. A flowchart of eligible individuals is displayed in Figure 1.

We used the National Registry of Deaths (NRD) [11] to document causes of death for the three sibling groups. The NRD contains information from all Danish death certificates since 1943, coded according to the Danish version of International Classification of Diseases [ICD-8 from 1972 through 1993, and ICD-10 from 1994 through 2001].

We followed the siblings from age 20 until death, emigration, or their 50th birthday, whichever came first. All subjects were censored after 31 December 2001, the latest date when electronically coded causes of death were available in the NRD. In the current study, the number of siblings, person years of follow-up, and number of deaths were slightly smaller than in our earlier study of mortality among siblings of HCV/HIV-co-infected patients, in which follow up was censored on 1 May 2005 [8]. Figure 1 displays a summary of the study design for selection of siblings.

We classified causes of death into five groups, based on death certificate information:

1. Alcohol or drug abuse-related;
2. HIV (excluding those related to substance abuse);
3. Natural causes (excluding those related to HIV or substance abuse);
4. Unnatural causes (including deaths due to accidents, suicide, or homicide and excluding deaths related to substance abuse);
5. Unknown causes.

To capture deaths related to abuse of alcohol and drugs (including some prescription drugs), we used diagnoses for both the underlying (main) and contributory causes of death. The causes of death defined as substance-abuse related were: a) mental disorders associated with alcohol or drug dependence (ICD-8: 291, 303, or 304. ICD-10: F10-F19); b) toxic effect of/poisoning by alcohol (ICD-8: E860, N979, or N980. ICD-10: X45, T51, or Y15); c) non-mental diseases caused by alcohol (ICD-8: 5710, 5711, or 5771. ICD-10: G312, G621, G721, I426, K292, K70, or K860); and d) toxic effect of/poisoning by specified psychoactive drugs

[accidental, suicidal or undermined whether accidentally or purposely inflicted] (ICD-8: E8530, E8540, or, E950 or E980 in combination with N9650, N9780, or N9790. ICD-10: X41, X42, or X60-X64 in combination with T40, Y11, Y12) [12]. For all other causes (group 2-5), only the underlying cause of death was used. In the Danish versions of ICD-8 and ICD-10, deaths with HIV as the underlying cause are coded as 0797 and B20-B24, respectively.

Among individuals with HIV as the underlying cause of death, the route of infection was identified from DHCS records. Deaths in those who were intravenous drug users were reclassified as a IDU-related death in a supplementary analysis, as proposed by Schulz-Schaeffer *et al.* [13]. We also performed a supplementary analysis of deaths with HCV infection or other liver diseases as the underlying cause of death.

For the three groups of siblings, we first computed total and cause-specific mortality rates (MR) by person-year analyses and used exact poisson confidence intervals. We then calculated total and cause-specific absolute excess mortality rates (EMR), comparing siblings of HIV-mono-infected and HIV/HCV-co-infected patients with siblings of population controls (the reference group). We calculated absolute EMR as the risk difference between two groups as described by Rothman [14] i.e. by subtracting the MR of siblings of population controls from the MR for siblings of each of the other two groups. We calculated 95% confidence intervals for the EMRs by using the standard error of the rate difference as described by Rothman [14,15]. We used Stata software, version 9.2 (StataCorp, College Station, TX, USA) for statistical analyses. The study was approved by the Danish Data Protection Agency.

RESULTS

Patients, population controls and their siblings

As of 1 May 2005, DHCS included 4,261 Danish residents who were older than 16 years at the time of HIV diagnosis. We excluded 271 patients not living in Denmark at time of HIV diagnosis and 459 patients who were never tested for HCV. Of the remaining 3,531 patients, 673 had HIV/HCV co-infection and 2858 were HIV-mono-infected. Owing to an insufficient number of eligible controls in some municipalities, the study included a mean of 95.3 population controls per HIV patient, yielding 336,652 matched controls. The HIV/HCV co-infected patients had 436 siblings, the HIV mono-infected patients had 1,837 siblings, and the population controls had 281,221 siblings. Nine families included two siblings with HIV. Hence, 18 persons were included as both HIV patients and siblings of HIV patients.

Mortality rates of siblings

The 436 siblings of HIV/HCV-co-infected individuals contributed 7,199 person-years of follow-up (PYR), followed from age 20 years. During this time we observed 29 deaths [MR = 4.03 per 1,000 PYR] (Table 1). Eighteen deaths were substance abuse-related [MR = 2.50 per 1,000 PYR]. The 1,837 siblings of HIV-mono-infected individuals contributed 31,232 PYR and 50 deaths [MR = 1.60 per 1,000 PYR], with 14 deaths [MR = 0.45 per 1,000 PYR] attributable to substance abuse. Finally, the 281,221 siblings of population controls contributed 4,590,754 PYR and 4,588 deaths [MR = 1.00 per 1,000 PYR], of which 1,169 deaths [MR 0.25 per 1,000 PYR] were substance abuse-related.

Excess mortality rates of siblings

Total and cause-specific MR and EMR with 95% confidence intervals for all groups of siblings are displayed in Table 1. The all-cause EMR for siblings of HIV/HCV-co-infected individuals was 3.03 per 1,000 PYR, compared with siblings of population controls. This excess mortality was mainly caused by substance abuse-related deaths (EMR = 2.25 per 1000 PYR) and to a lesser extent by unnatural deaths (EMR = 0.67 per 1,000 PYR) and by deaths with HIV as the underlying cause (EMR = 0.39 per 1,000 PYR).

Siblings of HIV-mono-infected individuals had an all-cause EMR of 0.60 per 1,000 PYR compared with siblings of population controls. This small excess mortality was due to deaths from an unknown cause (EMR = 0.28 per 1,000 PYR), deaths from substance abuse (EMR = 0.19 per 1,000 PYR), and unnatural deaths (EMR = 0.18 per 1,000 PYR).

Substance abuse in HIV-related deaths

Three siblings of HIV/HCV-co-infected individuals and 137 control siblings had HIV as their underlying cause of death. Of these, two siblings of HIV/HCV-co-infected individuals and four control siblings were registered in DHCS with IDU as the route of HIV transmission. When these deaths were counted as substance abuse-related deaths, the cause-specific mortality rate for siblings of HIV/HCV-co-infected individuals increased from 2.50 to 2.78 per 1,000 PYR, and the EMR increased from 2.25 to 2.52 per 1,000 PYR. The substance abuse-related mortality rate for controls changed slightly from 0.25 to 0.26 per 1,000 PYR.

HCV-related deaths

No siblings of HIV/HCV-co-infected patients had acute or chronic HCV infection or any other liver-related diagnosis as the underlying cause of death.

DISCUSSION

Our nationwide study showed that the increased mortality in siblings of HIV/HCV-co-infected patients is mainly caused by alcohol and drug abuse-related deaths. The study did not provide evidence that hepatitis C infection or increased inherited susceptibility to other infectious diseases contribute to the excess mortality in siblings of HIV/HCV co-infected patients.

These results lend credence to the hypothesis that excess mortality in HIV/HCV-co-infected patients, compared to HIV mono-infected patients, partly stems from factors other than the HCV disease itself, and a large part of the increased mortality in HIV/HCV co-infected patients - compared to HIV mono-infected patients - may be caused by similar family-associated and lifestyle-related factors. In the co-infected patients, substance abuse and associated risk behaviors may directly affect mortality. Indirectly, mortality in HIV/HCV-co-infected patients may be elevated by suboptimal health-seeking behavior, poor adherence to medical treatment, drug- or alcohol-related comorbidity, or health care providers' inattention to these patients. In addition, clinicians may choose to postpone antiretroviral therapy in HIV/HCV-co-infected patients due to concerns about behavioral factors or liver toxicity, despite evidence that early treatment initiation is beneficial for these patients [16].

The mechanisms underlying clustering of substance abuse-related deaths in families of HIV/HCV-co-infected individuals require better understanding. A likely explanation is that the common childhood and environment among siblings lead to a similar high risk of substance abuse. However, adoption and twin studies have shown that in addition to family environment, there is a strong genetic contribution to a familial predisposition for substance abuse [17,18]. In any case, familial clustering of the detrimental effects of substance abuse underscores the need for

Table 1. Total and cause-specific MR and excess MR among the three groups of siblings.

Causes of deaths in sibling groups	Number of deaths	Person-years	MR per 1000 PY (95% CI)	Excess mortality rates (95% CI)
Total				
Control	4588	4,590,754	1.00 (0.97–1.03)	
HIV	50	31,232	1.60 (1.19–2.11)	0.60 (0.16–1.05)
HIV/HCV	29	7,199	4.03 (2.70–5.79)	3.03 (1.56–4.50)
Substance abuse				
Control	1169	4,590,754	0.25 (0.24–0.27)	
HIV	14	31,232	0.45 (0.25–0.75)	0.19 (−0.04–0.43)
HIV/HCV	18	7,199	2.50 (1.48–3.95)	2.25 (1.09–3.40)
Unnatural causes				
Control	1,381*	4,590,754	0.30 (0.29–0.32)	
HIV	15**	31,232	0.48 (0.27–0.79)	0.18 (−0.06–0.42)
HIV/HCV	7***	7,199	0.97 (0.39–2.00)	0.67 (−0.05–1.39)
HIV				
Control	137	4,590,754	0.03 (0.03–0.04)	
HIV	2	31,232	0.06 (0.01–0.23)	0.03 (−0.05–0.12)
HIV/HCV	3	7,199	0.42 (0.09–1.22)	0.39 (−0.08–0.86)
Natural causes				
Control	1,547	4,590,754	0.34 (0.32–0.35)	
HIV	8	31,232	0.26 (0.11–0.50)	−0.08 (−0.26–0.10)
HIV/HCV	1	7,199	0.14 (0.00–0.77)	−0.20 (−0.47–0.07)
Unknown mode/cause of death				
Control	354	4,590,754	0.08 (0.07–0.09)	
HIV	11	31,232	0.35 (0.18–0.63)	0.28 (0.07–0.48)
HIV/HCV	0	7,199	0 †	−0.08†

*649 accidents, 618 suicides, 69 homicides, 45 injuries undetermined whether accidentally or purposely inflicted
**6 suicides, 9 accidents,
***3 suicides, 3 accidents, 1 injury undetermined whether accidentally or purposely inflicted
†Because there were no deaths from unknown causes in the HIV/HCV group, we were not able to calculate 95% confidence intervals (CI).
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adequate control groups, and/or extensive control of confounding when effects of HCV are investigated in epidemiological settings.

Further evaluation is also needed to determine whether these family-related risk factors have the same influence on prognosis in HCV-mono-infected patients, because HIV/HCV-co-infected individuals may represent a more vulnerable subgroup than HCV-mono-infected individuals. In line with our results, a large population-based study has recently demonstrated that young people with HCV infection have higher mortality from continued drug uses than from the HCV infection [19].

Our study had a number of strengths and limitations. Use of longitudinal population-based Danish registries permitted complete long-term follow-up with minimal selection bias, while the matched selection of siblings assured comparability of groups in terms of birth year and residency [8]. Because it has been shown that relying exclusively on underlying cause of death leads to underestimation of alcohol- and drug-related mortality, we used both underlying and contributory causes [12,13] to specify these causes of death. Still, death certificate data are not entirely accurate [20], and potential differential misclassification could lead to underestimation of the contribution of substance abuse to the category of unnatural deaths [13,21]. We could not assess mode of HIV infection in all HIV-related deaths among siblings of population controls. However, the resulting bias is probably negligible, since both the MR of HIV-related deaths and the proportion of HIV infections acquired by IDU among those with HIV-related deaths were small in this group. Finally, it is important to note that the results of this study may not be generalizable to settings where HIV/HCV-co-infected patients do not have IDU as the main route of transmission, for example Africa [22].

In conclusion, HCV co-infection among HIV-infected patients seemed to be a strong marker for family-related mortality due to substance abuse. In order to reduce morbidity and mortality in HIV/HCV co-infected patients, advances in antiviral treatment of HCV should be accompanied by interventions targeted at substance abuse and associated risk factors.

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Author Contributions

Conceived and designed the experiments: HS AH NL JG NO. Analyzed the data: AH NL. Wrote the paper: AH. Other: Interpretation of data: NO

NL JG HS. Critical revision of the paper for important intellectual content: NL JG GK AL CP HS NO. Data collection: JG GK AL CP NO AH.

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Genotypic drug resistance and long-term mortality in patients with triple-class antiretroviral drug failure

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Objective: To examine the prevalence of drug-resistance-associated mutations in HIV patients with triple-drug class virological failure (TCF) and their association with long-term mortality.

Design: Population-based study from the Danish HIV Cohort Study (DHCS).

Methods: We included all patients in the DHCS who experienced TCF between January 1995 and November 2004, and we performed genotypic resistance tests for International AIDS Society (IAS)-USA primary mutations on virus from plasma samples taken around the date of TCF. We computed time to all-cause death from date of TCF. The relative risk of death according to the number of mutations and individual mutations was estimated by Cox regression analysis and adjusted for potential confounders.

Results: Resistance tests were done for 133 of the 179 patients who experienced TCF. The median number of resistance mutations was eight (interquartile range 2–10), and 81 (61%) patients had mutations conferring resistance towards all three major drug classes. In a regression model adjusted for CD4$^+$ T-cell count, HIV RNA, year of TCF, age, gender and previous inferior antiretroviral therapy, harbouring ≥9 versus ≤8 mutations was associated with increased mortality (mortality rate ratio [MRR] 2.3 [95% confidence interval (CI) 1.1–4.8]), as were the individual mutations T215Y (MRR 3.4 [95% CI 1.6–7.0]), G190A/S (MRR 3.2 [95% CI 1.6–6.6]) and V82F/A/T/S (MRR 2.5 [95% CI 1.2–5.3]).

Conclusions: In HIV patients with TCF, the total number of genotypic resistance mutations and specific single mutations predicted mortality.

Introduction

Virological failure to all three major drug classes (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs] and protease inhibitors [PIs]), that is, triple-class failure (TCF), in HIV patients is an important clinical problem and is associated with a poor prognosis [1,2], with CD4$^+$ T-cell count and plasma HIV RNA (viral load [VL]) at time of TCF as independent prognostic factors for death [3]. Virological failure is associated with development of drug resistance [4]. Therefore, patients with TCF are likely to harbour multiple drug resistance mutations. A few studies have examined the association between resistance mutations and mortality in treatment-experienced patients [5–7]. Lucas *et al.* [7] found no association between the number of resistance mutations and mortality, whereas Zaccarelli *et al.* [6] found that mortality was associated with multiple-drug class-wide resistance. Most attempts to clarify the association between resistance mutations and clinical outcome have been hampered by convenience sampling (that is, including only patients in whom resistance testing was performed for reasons other than inclusion in the study), and no previous studies have examined the association between resistance mutations and clinical outcome in a population of patients with TCF. Therefore, the goals of the present study were to (i) examine the prevalence of mutations in patients with

TCF and (ii) examine how resistance mutations influence long-term mortality in TCF patients, while controlling for other prognostic factors.

Materials and methods

The Danish HIV Cohort Study (DHCS)

DHCS is a prospective, nationwide, population-based cohort study of all HIV-infected individuals treated in Danish HIV clinics since 1 January 1995 [8]. The study is ongoing, with continuous enrolment. HIV treatment in Denmark is restricted to eight specialized centres, and the Danish health care system provides free tax-supported medical care, including antiretroviral treatment. Updates of the study cohort are performed annually. Complete data on all patients seen in any of the centres since 1 January 1995 have been collected from patient files and entered into the DHCS database.

Virological failure

TCF was defined as in a previous study [1]. Virological failure was defined as a VL>1,000 copies/ml for a total of 120 days (not necessarily successive) while receiving treatment with a given class of drug. Periods of treatment interruptions, whether physician- or patient-initiated, were not counted as failure time. VL was defined as >1,000 copies/ml during the period between two consecutive VL measurements >1,000 copies/ml. Failure of a drug class could occur whether it was administered alone or as part of a multidrug regimen. The time that TCF occurred was the date the patient met the failure requirements for three drug classes. All DHCS patients that experienced TCF up to 1 November 2004 were eligible for the study.

Genotyping

We performed genotypic resistance tests for International Aids Society (IAS)-USA 2005 primary drug resistance mutations [9] on virus from plasma samples taken during a period 1 month before to 6 months after the date of TCF. We chose this interval to ensure that resistance mutations were also present on the date of TCF. On the basis of our dynamic definition of virological failure, the date of TCF typically occurs at a time between two dates of VL measuring. Consequently, samples were rarely available for that specific date.

Mortality data

Dates of death and migration were obtained from patient files and confirmed by the Civil Registration System [10]. Causes of death were registered in DHCS and were divided into HIV-related (AIDS-defining illnesses and bacterial infections), non-HIV related (other causes) and unknown.

Statistical methods

Follow up began at the date of TCF onset (baseline) and continued until death, last clinic visit or 1 May 2006. We computed Kaplan–Meier survival curves for the patients according to the main study variables. The relative risk of death associated with individual mutations, and the number of mutations (that is, more than versus fewer than the median) were estimated by Cox proportional hazard analysis. The influence of the following covariates on mortality estimates was evaluated in bivariate models, and in a model including them all: $CD4^+$ T-cell count at baseline (<50, 50–200 or >200 cells/μl) or time-updated $CD4^+$ T-cell count, carrying forward the most recent observation; $\log_{10}$ VL at baseline (<4, 4–5, >5 $\log_{10}$ copies/ml); gender; age at baseline; being antiretroviral-drug-naive prior to initiating highly active antiretroviral therapy (HAART); and year of TCF onset. As proposed by others [11], the influence of individual mutations was not assessed if the mutation was present in <10% of the study population. The proportional hazards assumption was tested based on Schoenfeld residuals and was found to be appropriate. Interactions of key variables were examined by stratified analyses. Patient characteristics were compared with χ^2 test and Student's *t*-test. A significance level of 0.05 was used for all analyses. Analyses were performed using Stata (College Station, TX, USA) statistical software, version 9.2.

Approvals and permissions

The study was approved by the Danish Data Protection Agency. Because the study did not entail any interaction with patients, it was not necessary to obtain patient consent or approval from the ethics committee.

Results

Study population

HAART was initiated in 2,797 DHCS patients during the study period. The median time of follow up after HAART initiation was 4.1 years (interquartile range [IQR] 1.9–6.3).

One-hundred and seventy-nine patients developed TCF. For 133 of those patients, a resistance test, done within the required interval surrounding the date of TCF, was available. Twenty-nine percent of the tests were done within 1 month of the date of TCF, and 74% were done within 3 months. Only one patient experienced TCF after 2001. At the time of TCF, the mean number of days with failure while on HAART for each drug class was 754 days for NRTIs, 167 days for NNRTIs and 688 days for PIs. Comparison of the 133 patients with and the 46 patients without an available resistance test revealed a significant difference in a

Table 1. Patient characteristics

Characteristics	Patients with resistance test	Patients without resistance test	*P*-value*
Total, *n* (%)	133 (100)	46 (100)	
Male gender, *n* (%)	101 (76)	34 (74)	0.783†
ART-naive at initiation of HAART, *n* (%)	24 (18)	14 (30)	0.077†
Risk exposure, *n* (%)			
MSM	71 (53)	22 (48)	0.573†
Heterosexual contact	45 (34)	15 (33)	
IDU	5 (4)	4 (9)	
Other	12 (9)	5 (11)	
AIDS before initiation of HAART, *n* (%)	65 (49)	17 (37)	0.162†
Race, *n* (%)			
Caucasian	109 (82)	35 (76)	0.510†
Black African	20 (15)	8 (17)	
Other	4 (3)	3 (7)	
Year of TCF, *n* (%)			
1997	24 (18)	5 (11)	0.241†
1998	32 (24)	15 (33)	
1999	37 (28)	16 (35)	
2000	29 (22)	6 (13)	
2001	10 (8)	2 (4)	
2002	1 (1)	1 (2)	
2003	0 (0)	1 (2)	
$CD4^+$ T-cell count at initiation of HAART‡, cells/μl	80 (30–170)	100 (22–220)	0.363§
$CD4^+$ T-cell count at time of TCF‡, cells/μl	194 (88–340)	180 (80–310)	0.643§
Log_{10} VL at initiation of HAART‡, cells/μl	5.2 (4.3–5.6)	5.1 (4.1–5.4)	0.553§
Log_{10} VL at time of TCF‡, cells/μl	4.3 (3.7–4.9)	3.9 (3.5–5.0)	0.376§
Age at initiation of HAART‡, cells/μl	36.8 (30.1–46.4)	38.9 (34.1–43.9)	0.734§
Age at time of TCF‡, years	40.0 (33.2–49.3)	42.8 (37.4–46.0)	0.609§
Mean time with failure, days			
NRTI	754	696	0.373§
NNRTI	167	192	0.010§
PI	688	610	0.230§

*Comparison of patients with and without resistance test. †χ^2 test. ‡Values given as median (interquartile range). §Student´s *t*-test. ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; IDU, intravenous drug users; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TCF, triple-class failure; VL, viral load.

single variable: number of days with NNRTI failure (167 days versus 192 days, *P*=0.01) (Table 1).

Resistance pattern

The 133 patients with an available resistance test had a mean of 6.3 mutations (median 8; IQR 2–10), including 3.6 NRTI-associated mutations, 1.3 NNRTI-associated mutations and 1.4 primary PI-associated mutations. Of those patients 127 (95%) had ≥1 drug resistance mutation. If only primary PI mutations were counted, the number of patients with ≥1 resistance mutation was 117 (88%). One-hundred and one (76%) of the patients had resistance mutations to ≥2 drug classes, and 81 (61%) had resistance mutations towards all three major drug classes. The frequency of individual resistance mutations is shown in Table 2. The six most frequent NRTI-associated mutations observed were at codons 215 (60%), 184 (50%), 41 (49%), 67 (40%), 210 (35%) and 219 (29%). The most frequent NNRTI-associated mutations were at codons 103 (53%) and 181 (25%), and the most frequent primary PI-associated mutations were at codons 90 (41%), 82 (33%), 46 (30%) and 84 (14%).

Mortality after TCF

The median time of follow up of the 179 patients after baseline was 4.3 years (IQR 2.8–5.5). The mortality rate after baseline was 70 (95% confidence interval [CI] 54–92) per 1,000 person-years (PYR), as opposed to an overall mortality in DHCS after initiation of HAART of 29 (95% CI 26–32) per 1,000 PYR. Patients in the upper half, harbouring ≥9 mutations, had increased mortality compared with patients harbouring ≤8 mutations (MRR 2.3; 95% CI 1.2–4.3) (Table 3; Figure 1). None of the other covariates

examined changed the estimated regression coefficient more than 15%, and in the full adjusted model the MRR remained at 2.3 (95% CI 1.1–4.8).

Other prognostic factors for death were CD4+ T-cell count at baseline (50–200 versus >200, MRR 2.9 [95% CI 1.4–6.2]; <50 versus >200, MRR 7.5 [95% CI

Table 2. Mutations present at time of TCF and their association with mortality

Position	Patients with mutation, *n* %	Distribution of individual mutations (*n* patients)	Cox regression analysis of time to all-cause death after TCF					
			Unadjusted			Adjusted*		
			MRR	95% CI	*P*–value	MRR	95% CI	*P*–value
NRTI								
T215C/E/F/I/V/Y	80 (60)	C (2), E (1), F (13), I (2), V (2), Y (60)	1.9	0.9–4.0	0.071	1.9	0.9–4.2	0.110
T215Y mutation only	60 (45)	Y	2.8	1.4–5.3	0.003	3.4	1.6–7.0	0.008
T215F mutation only	13 (10)	F	0.6	0.2–2.0	0.413	0.4	0.1–1.5	0.184
M184V/I	66 (50)	I (3), V (63)	0.8	0.5–4.6	0.605	0.9	0.5–1.8	0.847
M41L	65 (49)	L (65)	2.2	1.1–4.4	0.020	1.8	0.8–3.9	0.138
D67N	53 (40)	N (53)	1.0	0.5–1.9	0.980	0.9	0.4–1.7	0.656
L210W	47 (35)	W (47)	2.0	1.1–3.8	0.028	1.8	0.9–3.6	0.114
K219Q/E	38 (29)	E (16), Q (22)	0.7	0.3–1.4	0.264	0.5	0.2–1.0	0.054
K70R	33 (25)	R (33)	0.6	0.3–1.3	0.211	0.5	0.2–1.1	0.098
L74V	31 (23)	V (31)	1.5	0.8–2.9	0.228	1.9	0.9–3.9	0.074
V118I	25 (19)	I (25)	2.3	1.1–4.7	0.019	1.9	0.9–4.1	0.083
T69D/N	21 (16)	D (11), N (10)	1.0	0.4–2.4	0.988	0.7	0.3–1.7	0.429
E44D	18 (14)	D (18)	2.4	0.5–4.8	0.019	2.0	0.9–4.3	0.079
NRTI (MDR)								
A62V	2 (2)	V (2)	–	–	–	–	–	–
NNRTI								
K103N	71 (53)	N (71)	0.8	0.4–1.5	0.444	1.0	0.5–1.9	0.927
Y181C/I	33 (25)	C (28), I (5)	2.0	1.6–3.8	0.033	1.6	0.8–3.4	0.179
G190A/S	26 (20)	A (21), S (5)	3.0	1.6–5.8	0.001	3.2	1.6–6.6	0.002
L100I	17 (13)	I (17)	1.2	0.5–2.9	0.691	1.5	0.6–3.8	0.398
V108I	12 (9)	I (12)	–	–	–	–	–	–
V106A/M	8 (6)	A (3), M (5)	–	–	–	–	–	–
Y188L/C/H	7 (5)	C (1), H (1), L (5)	–	–	–	–	–	–
P225H	3 (2)	H (3)	–	–	–	–	–	–
Primary PI								
L90M	54 (41)	M (54)	1.0	0.5–1.9	0.987	1.0	0.5–2.0	1.000
V82F/A/T/S	44 (33)	A (30), F (4), S (3), T (7)	1.8	1.0–3.4	0.058	2.5	1.2–5.3	0.018
M46I/L	40 (30)	I (33), L (7)	1.1	0.6–2.2	0.677	1.0	0.5–2.0	0.989
I84V	18 (14)	V (18)	1.0	0.4–2.4	0.959	0.8	0.3–2.1	0.694
G48V	6 (5)	V (6)	–	–	–	–	–	–
D30N	6 (5)	N (6)	–	–	–	–	–	–
N88D/S	4 (3)	D (2), S (2)	–	–	–	–	–	–
L33F	3 (2)	F (3)	–	–	–	–	–	–
V32I	2 (2)	I (2)	–	–	–	–	–	–
I47V	2 (2)	V (2)	–	–	–	–	–	–
I50V/L	1 (1)	V (1)	–	–	–	–	–	–
No major resistance mutations	16 (12)							
One class	16 (12)							
Two classes	20 (15)							
Three classes	81 (61)							

The following International AIDS Society mutations were not detected in any of the study patients: K65R, Y115F, T69(SXX), V75I, F77L, F116Y, Q151M, M230L and P236L. Mortality rate ratio (MRR) was estimated only for those mutations present in ≥10% of the study patients. *Adjusted for CD4+ T-cell count, $\log_{10}$VL, age at baseline, gender, year of triple class failure (TCF) and being antiretroviral therapy (ART)-naive at initiation of highly active ART. CI, confidence interval; MDR, multidrug resistance mutations; NNRTI, non-nucleoside reverse transcriptase inhibitor mutations; NRTI, nucleoside reverse transcriptase inhibitor mutations; PI, protease inhibitor mutations; VL, viral load.

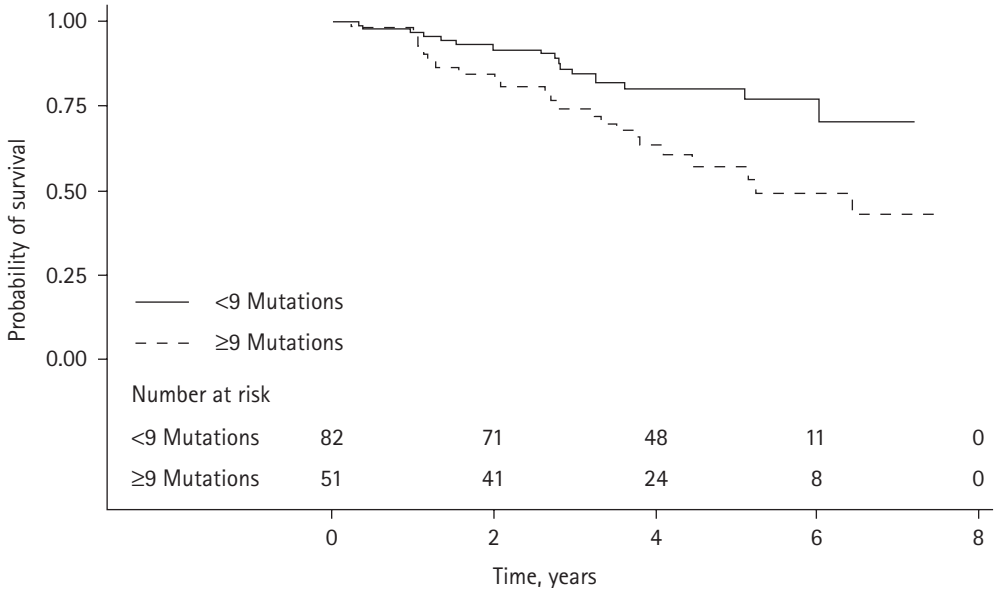
3.5–16.1]), log_{10} VL at baseline (<4 versus 4–5, MRR 1.8 [95% CI 0.9–1.8]; <4 versus >5, MRR 3.6 [95% CI 1.7–7.5]), male gender (MRR 2.8 [95% CI 1.2–6.7]) and year of TCF (MRR 0.7 per additional year [95% CI 0.6–0.9]) (Table 3). In the adjusted model, only the number of mutations and CD4+ T-cell count at baseline (50–200 versus >200, MRR 3.6 [95% CI 1.5–8.8]; <50 versus >200, MRR 8.6 [95% CI 3.0–24.7]), remained significant predictors of death (Table 3). When CD4+ T-cell count was entered as a time-updated variable, however, the prognostic value of number of mutations at baseline became insignificant (≥9 versus ≤8 mutations, MRR 1.4 [95% CI 0.7–2.9]), while CD4+ T-cell count remained a predictor (50–200 versus >200,

Table 3. Mortality after TCF

	Unadjusted			Adjusted		
	MRR	95% CI	*P*-value	MRR	95% CI	*P*-value
Number of mutations						
≤8	1	–	–	1	–	–
≥9	2.3	1.2–4.3	0.009	2.3	1.1–4.8	0.020
CD4+ T-cell count at baseline						
>200	1	–	–	1	–	–
50–200	2.9	1.4–6.2	0.005	3.6	1.5–8.8	0.005
<50	7.5	3.5–16.1	<0.001	8.6	3.0–24.7	<0.001
Log_{10} VL at baseline						
<4	1	–	–	1	–	–
4–5	1.8	0.9–1.8	0.100	1.2	0.5–2.9	0.722
>5	3.6	1.7–7.5	0.001	1.3	0.4–3.9	0.629
Year of TCF	0.7	0.6–0.9	0.007	1.1	0.8–1.5	0.609
Age at baseline (per year)	1.0	1.0–1.0	0.170	1.0	1.0–1.1	0.124
ART-naive at HAART initiation	0.8	0.4–1.6	0.467	1.6	0.5–4.6	0.403
Male gender	2.8	1.2–6.7	0.016	2.0	0.7–5.9	0.200

Cox regression analysis of time to all-cause death after triple-class failure (TCF). ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; MRR, mortality rate ratio; VL, viral load.

Figure 1. Kaplan-Meier survival curve. Time to all-cause death after triple-class virological failure (TCF), according to the number of genotypic drug resistance mutations at baseline (time of TCF)



MRR 3.1 [95% CI 1.2–8.0]; <50 versus >200, MRR 9.9 [95% CI 3.9–25.4]) (Table 4).

The following individual mutations were significantly associated with increased mortality in the adjusted model (Table 2): G190A/S, MRR 3.4 (95% CI 1.6–7.0); T215Y, MRR 3.2 (95% CI 1.6–6.6); and V82F/A/T/S, MRR 2.5 (95% CI 1.2–5.3). When these three mutations and number of mutations were included in the same regression model, the prognostic value of number of mutations (MRR 0.9 [95% CI 0.4–2.3]) and V82F/A/T/S (MRR 1.1 [95% CI 0.5–2.7]) decreased, whereas $CD4^+$ T-cell count at baseline, T215Y and G190A/S remained marked and statistically significant prognostic factors for death (Table 4). Finally, when including time-updated $CD4^+$ T-cell count instead of $CD4^+$ T-cell count at baseline in that same model, only the T215Y mutation remained a prognostic factor for death (MRR 3.0 [95% CI 1.3–7.0]), along with the latest $CD4^+$ T-cell count (50–200 versus >200, MRR 3.0 [95% CI 1.1–7.9]; <50 versus >200, MRR 9.6 [95% CI 3.7–25.1]) (Table 4). Substituting the thymidine analogue mutation (TAM)-1 pattern [12,13] (M41L+L210W+T215Y present at the same time) for T215Y in the model gave similar and significant results (data not shown). No mutations were significantly associated with decreased mortality, and we found no association between mortality and the number of drug classes with resistance mutations (data not shown). Causes of death were 60% HIV-related, 30% non-HIV related and 10% unknown.

The above-mentioned Cox models included a large number of variables for a dataset with only 40 deaths. However, if the analyses were repeated without adjusting for $\log_{10}$ VL at baseline, age at baseline, gender, year of TCF and being antiretroviral-drug-naive before initiation of HAART, the resulting regression coefficients were of equal magnitude and equally statistically significant (data not shown). Intravenous drug use (IDU) was seen in only five persons (Table 1) and therefore not assessed as an independent risk factor. To explore the potential confounding effect, we added IDU to the four multivariate regression models, but observed no substantial change in regression coefficients or their precision (data not shown).

Discussion

In this population-based study we found that more than three of five HIV patients with TCF had resistance mutations to all three drug classes. Patients with a high number of drug resistance mutations had a 2.3-fold increased risk of death, independent of $CD4^+$ T-cell count at time of TCF. Furthermore, some specific mutations were associated with increased mortality.

Our study had a number of strengths. For instance, the population-based design allowed us to identify all patients with TCF in Denmark with complete follow up and extensive covariate data. We were able to identify resistance test results on most patients near the date of TCF. Follow up after TCF was long-term, loss of follow

Table 4. Mortality after TCF

	Adjusted for time-updated $CD4^+$ T-cell count*			Adjusted for influential individual mutations*			Adjusted for time-updated $CD4^+$ T-cell count and influential individual mutations*		
	MRR	95% CI	*P*-value	MRR	95% CI	*P*-value	MRR	95% CI	*P*-value
Number of mutations									
≤8	1	–	–	1	–	–	1	–	–
≥9	1.4	0.7–2.9	0.348	0.9	0.4–2.3	0.896	0.8	0.3–1.9	0.556
$CD4^+$ T-cell count at baseline									
>200	–	–	–	1	–	–	–	–	–
50–200	–	–	–	3.4	1.4–8.4	0.008	–	–	–
<50	–	–	–	10.5	3.6–30.5	<0.001	–	–	–
$CD4^+$ T-cell count, time-updated									
>200	1	–	–	–	–	–	1	–	–
50–200	3.1	1.2–8.0	0.020	–	–	–	3.0	1.1–7.9	0.026
<50	9.9	3.9–25.4	<0.001	–	–	–	9.6	3.7–25.1	<0.001
T215Y	–	–	–	3.0	1.3–7.4	0.014	3.0	1.2–7.0	0.014
G190A/S	–	–	–	2.7	1.2–6.4	0.023	1.7	0.7–3.9	0.228
V82F/A/T/S	–	–	–	1.1	0.5–2.7	0.760	0.8	0.4–1.9	0.656

Cox regression analysis of time to all-cause death after triple-class failure (TCF). *Further adjusted for $\log_{10}$ viral load (VL) and age at baseline, gender, year of TCF and being antiretroviral therapy (ART)-naive at initiation of highly active ART. CI, confidence interval; MRR, mortality rate ratio; VL, viral load.

up was minimal, and we evaluated a clear clinical endpoint: death.

Increased mortality in patients with greater numbers of resistance mutations could reflect a direct effect whereby resistance mutations cause lower susceptibility to antiviral drugs and lead to faster disease progression. The effect of the most recent (time-updated) $CD4^+$ T-cell count on the relative risk estimates supports this theory, revealing an association between a high number of mutations at the time of TCF and subsequent low $CD4^+$ T-cell count. However, the T215Y mutation, part of the TAM-1 pattern [12,13], was a predictor of death at all time-updated $CD4^+$ T-cell count levels, indicating that the effect of mutations on mortality was indirect and exerted through mechanisms other than lowering of the $CD4^+$ T-cell count. The T215Y mutation is frequently generated during non-suppressive mono- or dual-NRTI therapy, which was restricted to patients with advanced HIV disease before HAART was a standard HIV treatment in Denmark. Thus, the T215Y mutation might be a marker for patients who were already immunodeficient in the early 1990s and not only a marker for cross-resistance to the NRTI class of drug. The T215Y mutation is also a marker for the TAM-1 pattern, which is associated with more extensive cross-resistance [14], longer use of HAART [15] and greater relative fitness [16] than the TAM-2 pattern.

It is reassuring that, in our study of TCF, one mutation from each of the three drug classes was associated with mortality, independent of the total number of mutations. All three mutations are associated with a number of other mutations. For instance 215Y is associated with mutations in positions 41, 44, 67, 118 and 210 [20]; G190A/S is associated with mutations in position 181 of the reverse transcriptase gene [21]; and V82A is associated with mutations in positions 46 and 48 of the protease gene [22]. The G190A/S mutation [21] has been observed primarily during therapy with nevirapine, didanosine and zidovudine, an outdated combination; the V82F/A/T/S mutation confers resistance to regimens such as ritonavir and indinavir [23], as well as to ritonavir-boosted saquinavir [9]. Thus, all three mutations are associated with exposure to antiretroviral regimens rarely used anymore. In summary, mutations and mortality seemed to be associated with previous non-suppressive therapy, longer duration of HIV infection and more advanced early disease. Thus, the mutations could be proxies for unmeasured factors known to be associated with poor survival. Another factor could be low compliance to treatment regimens, which is associated with increased mortality through coexisting conditions like mental illness and substance abuse [17–19], and presumably also through non-compliance to other essential therapies. On the other hand the assumption that hard-core non-compliers failing with wild-type virus fared worst was not supported by our data. Other potential confounders could be inferior HIV care and/or treatment by inexperienced physicians, but this would be unlikely in our setting where treatment and care is free and limited to specialized clinics. Hence, these numerous identified or potential associations might all be contributory causes to the observed mortality, but no conclusion can be made from our data.

Drug-resistant HIV can be less fit than wild-type virus [24], and cross-sectional studies have found a U-shaped association between the number of resistance mutations and plasma concentrations of HIV RNA, suggesting that an increasing number of mutations will eventually overcome the reduced fitness that allows virological suppression at lower levels of resistance [11,25]. Twelve percent of our patients had no resistance mutations detected at the time of TCF. Some of these patients could be totally non-compliant, fulfilling our criteria for virological failure without ever taking drugs that would induce resistance mutations. In fact, the very low rate of transmitted resistance in Denmark [26,27] makes it likely that the majority of totally non-compliant patients will have no resistance mutations. In our follow-up study, these patients had plenty of time to improve compliance, which might explain why we did not find a similar U-shaped association between the number of mutations and mortality.

Previous studies of mutations and mortality [6,7,28] included only 14–19 patients with triple-class mutations, whereas in the present study 81 (61%) of the patients with confirmed TCF had major mutations to all three drug classes. Thus, our data suggest that the virological failure model [2,3] captures patients in whom viral resistance is an essential component of the failure.

Because we analysed a fairly large number of mutations (that is, 21) the observed effect of individual mutations might be a chance finding. However, the panel of mutations that we analysed were selected by the IAS-USA and on the basis of biological relevance [9], and we used a minimum prevalence criterion of 10% as suggested by others [11].

Our study has some further limitations. Firstly, resistance tests within the analytical window were available for only 133/179 patients with TCF. However, comparison of characteristics of the two groups revealed no significant differences, making major bias in selection unlikely. Secondly, the number of resistance mutations we detected is likely to be an underestimation, because particular mutations selected during previous antiretroviral regimens might go undetected when the test is performed without

pressure on the mutation in question. However, the number of undetected mutations is assumed to be similar in all patients, because all were triple-drug-class-experienced and would, therefore, previously have been exposed to drugs not included in their regimen at the time of resistance testing. Thus, this information bias would probably not affect the association between mortality and the number of mutations. Thirdly, with only 40 deaths, the study was not large enough for more advanced analyses. For example, we could not analyse the effect of rare resistance mutation patterns or the effect of individual drug combination regimens in association with different resistance mutations. Nor did we analyse outcome in relation to the number of drugs to which the virus was sensitive because of frequent regimen switches and because being drug-resistant versus drug-sensitive in this scenario is often not an all-or-none phenomenon. Finally, the development and appearance of drug mutations depend on the drug combinations used and the order in which they are used. The vast majority of the failures occurred early in the study period, at a time when most PI regimens were unboosted, and our findings might not apply to patients experiencing TCF today, who would probably have a different treatment history. However, the prevalence and distribution of mutations in our study was comparable to that found in other studies [25].

We conclude that in patients with TCF the total number of genotypic resistance mutations and specific single mutations predict mortality and are associated with a further decline in $CD4^+$ T-cell count. The majority of these mutations appear to have accumulated during suboptimal therapies in the 1990s. When TCF occurs, resistance is an important contributor to the increased mortality associated with the condition. We await the introduction of further drug classes to see whether this will eliminate failure-related mortality, or whether we will face resistance to five or six drug classes in the future.

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