Table of Contents

SHM

De Stichting HIV Monitoring (SHM) werd op 11 november 2001 opgericht en op 1 mei 2002 geactiveerd. Zij is gevestigd te Amsterdam (KvK nr. 34160453). De SHM is door de Minister van Volksgezondheid, Welzijn en Sport aangewezen als de instantie die de registratie en monitoring van HIV-geïnfecteerden in de Nederlandse HIV-Behandelcentra uitvoert.

Het doel van de Stichting is 'een bijdrage te leveren aan de ontwikkeling van kennis over de epidemiologie en het beloop van zowel de behandelde als de onbehandelde infectie met HIV'. Om dit doel te bereiken ontplooit de Stichting een aantal activiteiten, zoals:

- Het verzamelen en beheren van geanonimiseerde gegevens van HIV-geïnfecteerde patiënten en hun antiretrovirale behandeling;
- het bewerken van gegevens ten behoeve van rapportage aan overheid en andere instanties over het verloop en de behandeling van de HIV-infectie;
- het beschikbaar stellen van gegevens aan HIV-geïnfecteerden en aan hun behandelaars;
- het beschikbaar stellen van gegevens ten behoeve van wetenschappelijk onderzoek en consensusvorming;
- het beschikbaar stellen van gegevens ter informatie aan de media en aan andere belangstellenden.

Inleiding

De Stichting HIV Monitoring (SHM) is in 2003 geleidelijk aan op haar volle personele sterkte gekomen. In het eerste kwartaal zijn de laatste organisatorische stappen gezet die nog met de activering van de SHM te maken hadden, zoals het afronden van de laatste contracten met de HIV-Behandelcentra en het consolideren van de financiële en administratieve organisatie. Hierdoor kon meer aandacht worden gegeven aan inhoudelijke ontwikkelingen. Dit heeft geresulteerd in de eerste wetenschappelijke publicaties en presentaties van de SHM en een uitvoerig wetenschappelijk verslag over HIV en AIDS in Nederland in december 2003 op basis van het SHM registratieprogramma. Het aantal aanvragen voor gebruik van gegevens uit de SHM database nam toe; de eerste resultaten van onderzoek dat met behulp van deze gegevens wordt uitgevoerd zijn zichtbaar. Nationale en vooral ook internationale samenwerking bleken productief en hebben inmiddels een meer structurele vorm gekregen.

Belangrijk voor de relatie tussen de HIV-Behandelcentra en de SHM was ook de invoering van een nieuw database-programma, dat noodzakelijk was geworden om de kwaliteit van de verzamelde en nog te verzamelen gegevens te kunnen garanderen. De implementatie van dit programma, Oracle Clinical, was aan het eind van 2003 bij het merendeel van de HIV-Behandelcentra afgerond, evenals de parallelle opleiding en training van dataverzamelaars. Bovendien werd een aantal nieuwe, vaste dataverzamelaars aangesteld en werd het relatief grote aantal tijdelijke krachten met succes teruggebracht. Tenslotte bleek 2003 een jaar van forse toename van het aantal geregistreerde HIV-patiënten: van 7.557 eind 2002 naar 8.999 per eind december 2003.

Tegelijkertijd werden belangrijke veranderingen in de epidemie zichtbaar: HIV-geïnfecteerden leven langer dan voorheen. Mede hierdoor stijgt het aantal patiënten dat met Highly Active Antiretroviral Therapy (HAART) wordt behandeld. Het aantal antivirale middelen in de HAART combinatie blijft vrijwel constant, net als de kosten per patiënt. Een andere verandering in de HIV-epidemie in Nederland was het toenemende aandeel van patiënten dat via heteroseksueel contact werd geïnfecteerd. Opmerkelijk is vooral dat de populatie afkomstig uit Zuidelijk Afrika in deze groep inmiddels groter is dan die van de autochtonen. De cijfers afkomstig van de HIV-Behandelcentra bevestigen trends die ook elders in West-Europa worden waargenomen, waaronder het groeiend aandeel relatief jonge vrouwen dat via heteroseksueel contact wordt besmet. Voornaamste afwijking van deze trends is de in Nederland nog steeds beperkte overdracht van resistente HIV-stammen.

Het aantal nieuwe patiënten dat in het observationele klinische SHM cohort wordt geïncludeerd neemt nog steeds toe. Dankzij de gemeenschappelijke inspanningen van dataverzamelaars, datamonitors en HIV-behandelaars in de HIV-Behandelcentra is inmiddels een omvangrijke gegevensverzameling beschikbaar van - al dan niet met antiretrovirale middelen behandelde - met HIV geïnfecteerde patiënten, die over een lange periode prospectief worden gemonitord. Deze gegevensverzameling kan met recht uniek genoemd worden, zeker in combinatie met het van deze patiënten verzamelde en bewaarde bloedplasma. Zij zal naar verwachting bijdragen aan het verwerven van een beter inzicht in het beloop van de epidemie en de behandeling van HIV in Nederland.

Amsterdam, 29 maart 2004

Dr. Frank de Wolf,
directeur SHM

Financieel verslag

Financieel verslag

Inkomsten

De op 4 september 2002 door het bestuur vastgestelde begroting van in totaal € 1,913,728 van de Stichting HIV Monitoring werd op 21 oktober 2002 door de Minister van Volksgezondheid, Welzijn en Sport goedgekeurd. Op basis van deze begroting werd op 20 januari 2003 de Beleidsregel HIV Monitoring vastgesteld door het College Tarieven Gezondheidszorg. Het daarin vermelde extra bedrag van € 86,988 werd toegewezen aan de budgetten van de 22 door de Minister erkende HIV-Behandelcentra en vervolgens door de SHM bij deze centra gedeclareerd.

Met betrekking tot de variabele kosten was in de begroting 2003 al rekening gehouden met 7.431 HIV-geïnfecteerde patiënten follow-up in elk van de HIV-Behandelcentra per 1 juli 2002 - en dus niet met het aantal bij de SHM geregistreerde patiënten. Het aantal per 31 december 2003 geregistreerde patiënten in follow-up bleek met 321 te zijn gegroeid ten opzichte van het aantal patiënten follow-up per medio 2002. De vaste kosten in de begroting 2003 werden op hetzelfde niveau gehouden als in de begroting voor 2002.

In 2003 werd de DAD studie (Data Collection on Adverse Events of Anti-HIV Drugs) ook administratief van IATEC overgenomen, waarvoor een vergoeding van € 102,414 werd ontvangen. Hiervoor werd een separate projectadministratie opgezet. Voor de DAD studie worden extra data-items verzameld met behulp van case report forms die op specifieke DAD events zijn afgestemd. Deze events worden voor 100% - in plaats van de binnen de SHM gebruikelijke 10% - gemonitord.

Uitgaven

De uitgaven hebben over het algemeen de daarvoor begrote posten gevolgd. Ten behoeve van de decentraal uitgevoerde dataverzameling en de hierop volgende data-invoer werd € 89 per patiënt aan de HIV-Behandelcentra uitgekeerd, behalve aan de centra die de uitvoering van deze taken hadden uitbesteed aan de SHM (AMC-UvA, OLVG, UMCL en Ziekenhuis Walcheren). In verband met de verzameling en opslag van patiëntmateriaal, van cruciaal belang voor de uitvoering van de opdracht aan de SHM over het monitoren van resistentie en het monitoren van veranderingen in de HIV-epidemie, werd in 2003 in totaal € 86,649 aan de HIV-Behandelcentra overgemaakt.

Veruit de grootste uitgaven hebben betrekking op de personeelskosten. Voor het jaar 2003 was, inclusief de door de SHM uitgevoerde decentrale dataverzameling, 18.6 fte begroot en gemiddeld 17,89 fte bezet, waarvan 2.0 fte niet in dienst van de SHM. Ten behoeve van de (decentrale) dataverzameling, datalogistiek en data-management werd in 2003 11.24 fte ingezet, 3.0 fte werd gebruikt voor bewerking en analyse van de verzamelde data en 3.65 fte voor de coördinatie en het dagelijkse management van de stichting. Belangrijke materiële kosten betreffen de licenties voor de database met de patiëntgegevens, het gebruik van het AMC-netwerk en de productie van de wetenschappelijke rapportages van de stichting.

De kosten door derden zijn in de loop van 2003 met een kwart teruggebracht, waarmee ook in de cijfers duidelijk wordt dat de SHM administratief in rustiger vaarwater is terechtgekomen. Tenslotte is in 2003 de rekening-courant bij het AMC grotendeels afbetaald.

Reserve

De financiële reserve van de SHM komt in 2003 uit op € 241,270. Er wordt naar gestreefd om deze reserve tot een zodanige omvang te laten groeien dat de salarissen van het personeel voor zes maanden kunnen worden gegarandeerd.

Balans per 31 december 2003 na bestemming resultaat

	2003 (€)	2002 (€)		2003 (€)	2002 (€)
ACTIVA			**PASSIVA**		
Vaste activa			**Eigen vermogen**		
Materiele vaste activa	0	0	Reserve aanvaardbare kosten	241.270	108.777
			Bestemmingsreserve investeringen	-	110.285
			Bestemmingsreserve DAD studie	92.340	-
	0	**0**		**333.610**	**219.062**
Vlottende activa			**Kortlopende schulden en overlopende passiva**		
Vorderingen en overlopende activa	7.167	764.533	Rekening-courant AMC	215.281	776.751
Liquide middelen	774.989	999.185	Nog af te rekenen met HIV-Behandelcentra	-	461.418
			Crediteuren	114.550	146.030
			Overige kortlopende schulden en overlopende passiva	118.715	160.457
	782.156	**1.763.718**		**448.546**	**1.544.656**
Totaal	**782.156**	**1.763.718**	**Totaal**	**782.156**	**1.763.718**

Resultatenrekening 2003

	Resultaat 2003 (€)	Begroting 2003 (€)	Resultaat 2002 (€)
Wettelijk budget voor aanvaardbare kosten	1.913.737	1.913.729	1.760.556
Subsidie DAD studie	102.412	0	0
Subsidie event-registratie DAD studie	7.905	0	0
Som der bedrijfsopbrengsten	**2.024.054**	**1.913.729**	**1.760.556**
Vergoeding materiaalopslag	86.649	86.002	74.817
Vergoeding dataverzameling	401.998	401.249	386.601
Vergoeding event-registratie DAD studie	7.905	0	0
Personeelskosten	1.066.323	1.026.653	816.585
Afschrijving materiele vaste activa	129.570	0	15.428
Overige bedrijfskosten	292.032	399.825	248.346
Som der bedrijfslasten	**1.984.477**	**1.913.729**	**1.541.777**
Bedrijfsresultaat	**39.577**	**0**	**218.779**
Financiële baten en lasten	22.552	0	283
Diverse baten en lasten	52.419	0	0
Som diverse baten en lasten	**74.971**	**0**	**283**
Resultaat	**114.548**	**0**	**219.062**

Organisatieverslag

Organisatieverslag

HIV-Behandelcentra

Per 1 januari 2003 verkreeg het Medisch Centrum Alkmaar erkenning als HIV-Behandelcentrum. Hiermee is het aantal centra uitgebreid tot 22. Vier academische HIV-Behandelcentra hebben, behalve een erkenning voor volwassen patiënten, ook een erkenning voor de behandeling van pediatrische HIV en AIDS. In totaal zijn er 24 ziekenhuislocaties betrokken bij de door de Minister van VWS erkende HIV-Behandelcentra:

Academisch Medisch Centrum bij de Universiteit van Amsterdam
Academisch Ziekenhuis Groningen
Leids Universitair Medisch Centrum
Academisch Ziekenhuis Maastricht
Universitair Medisch Centrum St. Radboud, Nijmegen
Universitair Medisch Centrum Utrecht
VU Medisch Centrum, Amsterdam
Erasmus Medisch Centrum, Rotterdam
St. Elisabeth Ziekenhuis, Tilburg
Kennemer Gasthuis Haarlem, locatie EG
Medisch Centrum Alkmaar
Medisch Spectrum Twente, Enschede
Onze Lieve Vrouwe Gasthuis, locatie Oosterpark, Amsterdam
Onze Lieve Vrouwe Gasthuis, locatie Prinsengracht, Amsterdam
Onze Lieve Vrouwe Gasthuis, locatie Jan van Goyen, Amsterdam
Slotervaart Ziekenhuis, Amsterdam
Medisch Centrum Haaglanden, locatie Westeinde, Den Haag
Leyenburg Ziekenhuis, Den Haag
Ziekenhuis Rijnstate, Arnhem
Medisch Centrum Leeuwarden
Ziekenhuis Walcheren, Vlissingen
Catharina Ziekenhuis, Eindhoven
Isala klinieken, locatie Sophia, Zwolle
Sint Lucas Andreas Ziekenhuis, Amsterdam

Wilhelmina Kinderziekenhuis UMCU, Utrecht
Emma Kinderziekenhuis AMC, Amsterdam
Sophia Kinderziekenhuis, EMC, Rotterdam
Academisch Ziekenhuis Groningen

Met elk van de HIV-Behandelcentra heeft de SHM een overeenkomst, waarin de verzameling wordt geregeld van demografische, epidemiologische, klinische, immunologische, virologische en farmacologische gegevens van patiënten met een HIV-infectie die in één van deze ziekenhuizen worden gevolgd.

Interne organisatie

Het bureau van de SHM is in 2003 gereorganiseerd om de organisatiestructuur beter af te stemmen op de taken die het moet uitvoeren. Er is een unit patiëntgegevens & kwaliteitscontrole (PG&QC) en een unit databewerking & -analyse (DBA). In de PG&QC unit zijn dataverzamelaars in dienst van de SHM ondergebracht en worden alle activiteiten met betrekking tot de dataverzameling gecoördineerd. Ook de datamonitors en de patiëntadministratie (inclusie/exclusie) zijn in deze unit opgenomen. Voorts wordt vanuit deze unit het datamanagement gecoördineerd, dat wordt uitgevoerd door Data Management Support (DMS) van de afdeling Klinische Epidemiologie en Biostatistiek (KEB) van het AMC. In de tweede helft van 2003 werd de leiding van de unit overgedragen aan de nieuw aangestelde manager PG&QC. De omvang van de PG&QC unit was per 31 december 2003 4.49 fte voor de datamonitoring, administratie, QC en coördinatie en 6.38 fte decentrale dataverzameling door SHM en 0.5 fte uitzendkrachten voor tijdelijke ondersteuning van de decentrale dataverzameling. Gedurende 2003 werd het aantal uitzendkrachten dat door de SHM werd ingezet bij de dataverzameling drastisch teruggebracht en vervangen door (vaak parttime) vaste krachten. Naast een kostenbesparing heeft dit vooral geleid tot behoud van binnen de organisatie beschikbare kennis en ervaring, wat van belang is voor de kwaliteit van de gegevensverzameling.

De DBA-unit bestaat uit 3.0 fte onderzoekers op het gebied van de epidemiologie, statistiek en mathematische en analytische modellen. Vanaf oktober 2003 werd 0.6 fte voor de duur van een half jaar aan de DBA-unit toegevoegd ten behoeve van het doen van een kostenanalyse van de behandeling van HIV-geïnfecteerden.

In het bureau van de SHM zijn tenslotte het secretariaat, de financiële en personele administratie & controlling, de in- en externe communicatie en de directie ondergebracht. Per eind december 2003 was daarmee in totaal 3.65 fte gemoeid.

Gegevensverzameling & QC verslag

Gegevensverzameling

De volgende gegevens worden verzameld:

Identificatie van geanonimiseerde patiëntgegevens (uniek codenummer)
Identificatie en codering van het HIV-Behandelcentrum en de internist/behandelaar
Gegevens van HIV transmissierisico's
Klinische gegevens van de HIV-infectie
Laboratoriumgegevens van de HIV-infectie
Klinische gegevens van eventuele overige infecties
Laboratoriumgegevens van eventuele overige infecties
Gegevens van antiretrovirale therapie
Resistentiegegevens van HIV-1
Klinische gegevens van bijwerkingen/toxiciteit van antiretrovirale therapie
Laboratoriumgegevens van bijwerkingen/toxiciteit van antiretrovirale therapie
Gegevens van co-medicatie

Voor de verzameling van data met betrekking tot resistentie werd een protocol ontwikkeld, waarbij nucleotide en aminozuur sequenties van het RT en protease gen van HIV aan de SHM kunnen worden verstrekt en vervolgens in een separate database worden opgeslagen. Het merendeel van de sequenties werd gegenereerd door één van de virologische laboratoria in het AMC, UMCU, EMR, LUMC, waar de meeste HIV-resistentiebepalingen in Nederland werden uitgevoerd, en door de virologische laboratoria van het UMCN-St. Radboud, het VUMC en het Centraal Laboratorium voor Bloedtransfusie in Amsterdam. Kwaliteitscontroles van resistentiebepalingen en het geregeld vernieuwen van interpretatieschema's voor nieuw gevonden (combinaties van) mutaties en nieuwe antiretrovirale middelen werd geregeld via de SHM-werkgroep Virologie.

Privacy

Gegevens van patiënten werden verzameld als onderdeel van hun reguliere follow-up en/of behandeling. Tegen opname van gegevens in de SHM database kon door de patiënt bezwaar worden aangetekend. Data van een patiënt werden opgeslagen onder een unieke code; behalve geslacht en geboortedatum zijn geen andere persoonsgebonden gegevens in de SHM monitoring database opgenomen.

SHM database & datamanagement

Eind 2002 werd begonnen met de implementatie van een nieuwe SHM database op basis van het op klinische trials georiënteerde software-pakket Oracle Clinical. Belangrijke overwegingen om van database te veranderen waren:

- Het kunnen handhaven en verbeteren van de kwaliteit van de ingevoerde patiëntgegevens over een lange periode van follow-up
- Het verbeteren van de veiligheid met betrekking tot de database en de daarin opgeslagen, geanonimiseerde patiëntgegevens
- Het verbeteren van de efficiëntie van de databewerking
- Het verbeteren van de privacy van de patiënten.

Het ontwikkelingsproces van nieuwe invoerschermen, aangepast aan de specifieke situatie van de follow-up van een observationeel cohort en het parallel optimaliseren van de database, hebben tot mei 2003 geduurd. Op 12 mei 2003 werd begonnen met het installeren van Oracle Clinical en de hiermee gepaard gaande instructie aan dataverzamelaars in de HIV-Behandelcentra. Bij de planning van de installatie en instructie werd zoveel mogelijk rekening gehouden met de beschikbaarheid van de dataverzamelaars, de ICT medewerkers

en de kwantiteit en kwaliteit van de dataverzameling in de behandelcentra. Gedurende 2003 werd Oracle Clinical op 20 van de 24 ziekenhuislocaties geïnstalleerd. Bij de resterende vier locaties (Catharina Ziekenhuis, Eindhoven; Universitair Medisch Centrum Utrecht; Medisch Spectrum Twente, Enschede; Ziekenhuis Rijnstate, Arnhem) werd de installatie uitgesteld tengevolge van technische problemen op de locaties. In 18 ziekenhuizen werden instructies gegeven aan de dataverzamelaars en in totaal werden 30 dataverzamelaars en 3 studenten ingewerkt en met de nieuwe database vertrouwd gemaakt. In 2003 werden bovendien 24 nieuwe dataverzamelaars en 4 studenten door de datamonitors van de SHM opgeleid en ingewerkt.

De geleidelijke invoering van de nieuwe database betekende uiteraard dat vanaf mei 2003 naast de nieuwe database de oude Microsoft Access database HIVREG nog in gebruik was en onderhouden moest worden. Dit had bovendien gevolgen voor de continuïteit van de data, waarvoor een aantal nieuwe administratieve procedures werd ontworpen. In samenwerking met de KEB werd een centrale Microsoft Access database opgebouwd waarin de data uit de HIVREG van alle ziekenhuizen opgenomen werden. Deze database wordt gebruikt om eventuele correcties centraal in oude data te verwerken, maar vooral ook voor de productie van de periodieke data merges en de dagelijkse updating van lokale Access-bestanden die sinds het ATHENA project in verschillende HIV-Behandelcentra bestaan. Die lokale bestanden vormen vaak de basis voor de presentatie van overzichten tijdens patiëntbesprekingen in de HIV-Behandelcentra.

Kwaliteitscontrole (QC)

Op 1 januari 2003 werd de steekproef voor 2003 gedaan van 10% van de al aangemelde patiënten en 10% van de nieuw aangemelde patiënten. Per 1 januari 2003 waren 5.910 patiënten aangemeld. Gedurende 2003 werden 593 daarvan gemonitord, inclusief 104 patiënten die ook in het kader van de DAD studie werden gemonitord in verband met een cardiovasculair accident (41) of in verband met overlijden (63). In totaal 100 nieuw aangemelde patiënten werden in 2003 voor het eerst gemonitord.

Source data verification werd bij in totaal 321 patiënten prospectief en 168 patiënten retrospectief uitgevoerd en gemiddeld werden de centra 6.7 keer bezocht door hun vaste SHM monitor. Tijdens de prospectieve monitoring van de al aangemelde patiënten bleek dat de kwaliteit van de data vaak slechter werd en soms ook retrospectieve monitoring nodig was. Dit hing ten dele samen met het aantal patiënten dat in een behandelcentrum werd gezien en was vaak locatie-specifiek. Bovendien hing de kwaliteit van de dataverzameling en de data-invoer samen met de inhoudelijke kennis van de dataverzamelaar: bij HIV/AIDS-consulenten en bij voor de SHM dataverzameling specifiek aangestelde medewerkers bleek deze vaak beter dan bij medewerkers die het verzamelen van data niet als hoofdtaak hebben en daarnaast niet HIV-gerelateerde, in omvang vaak grotere, taken moeten verrichten.

Dat de HIV-Behandelcentra in 2003 gemiddeld twee keer vaker dan in 2002 door een datamonitor werden bezocht, kwam vooral omdat een groot aantal nieuwe dataverzamelaars moest worden ingewerkt. Bij wijze van investering in de toekomstige kwaliteit van de data werden de trainingen en instructies zoveel mogelijk op locatie uitgevoerd.

Elk centrum kreeg een eigen SHM datamonitor. Bovendien werd geïnvesteerd in de communicatie tussen dataverzamelaar en datamonitor met als doel de consistentie van de dataverzameling nog verder te bevorderen. Het contact tussen de dataverzamelaars, datamonitors en de manager QC is door gebruik te maken van elektronische communicatie geïntensiveerd. Door gebruik van gegevens uit de nieuwe Oracle Clinical database ontstond tevens de mogelijkheid om na te gaan of en op welke punten een dataverzamelaar specifieke training en begeleiding nodig heeft. Datamonitors werden zo in staat gesteld om on-line data-specifieke discrepanties op te lossen.

In 2003 werd geleidelijk aan duidelijk dat de bestaande aan- en afmeldingprocedures te veel administratieve werkzaamheden met zich meebrengen en bovendien te weinig waren toegesneden op de relatief lange follow-up duur van patiënten. Het veranderen van HIV-behandelaar en het tijdelijk worden gevolgd in een ander HIV-Behandelcentrum blijken niet verankerd te zijn in deze procedure, die daarom aangepast zal moeten worden. Deze situatie heeft geleid tot de nodige misverstanden en problemen bij de bewerking en analyse van gegevens. Verbetering van de communicatie tussen de PG&QC en de DBA units heeft ertoe geleid dat onopgeloste discrepanties door de datamonitors met de desbetreffende HIV-Behandelcentra worden besproken en vanaf de tweede helft van 2003 effectief door source verification worden opgelost.

Verslag Monitoring

Registratie van HIV-geïnfecteerde volwassen patiënten

Het totaal aantal volwassen patiënten dat in 2003 cumulatief bij de SHM werd geregistreerd is 8.999 patiënten. Van deze patiënten zijn 8.317 (92.5%) geregistreerd als in leven en 682 (7.6%) als overleden. Per 31 december 2003 zijn van 7.752 (86.2%) patiënten gegevens verzameld, bij 679 (7.6%) patiënten is dit niet het geval (Tabel 1). De discrepanties per ziekenhuislocatie zijn relatief groot en worden beïnvloed door aanmerkelijke verschillen in de actualiteit van de invoer van patiëntgegevens. In 2003 hadden het AZM, het Erasmus Medisch Centrum Rotterdam, het VUMC en het ziekenhuis Leyenburg grote invoerachterstanden. Onze schatting is dat tussen de 3% en 5% daadwerkelijk lost to follow-up is. Uiteraard zijn van de 568 (6.4%) patiënten die zijn overleden vóór 1 januari 2003 geen recente gegevens verzameld.

De inclusie per ziekenhuislocatie over het jaar 2003 bedroeg in totaal 1.478 volwassenen (Tabel 2). Daarvan zijn er 36 (2.5%) overleden en werd bij 284 (19.3%) de diagnose AIDS gesteld. Van 152 (10.3%) zijn (nog) geen follow-up gegevens gemonitord. Ook hier zijn verschillen per ziekenhuislocatie zichtbaar en wordt de invoerachterstand bij het Erasmus Medisch Centrum wederom bevestigd.

HIV-Behandelcentrum	Geïncludeerd t/m 31-12-2003		In leven t/m 31-12-2003		Dood t/m 31-12-2003		Follow-up (incl. dood) t/m 31-12-2003		Geen follow-up na 31-12-2002		Dood voor 01-01-2003	
	N	%	N	%	N	%	N	%	N	%	N	%
AMC Amsterdam	1488	16.6	1366	91.8	122	8.2	1327	89.2	52	3.5	109	7.4
AZG Groningen	385	4.3	364	94.5	21	5.5	349	90.7	23	6	13	3.4
LUMC Leiden	287	3.2	271	94.4	16	5.6	265	92.4	9	3.2	13	4.6
AZM Maastricht	335	3.8	301	89.9	34	10.1	238	71.1	64	19.2	33	9.9
UMC St. Radboud Nijmegen	265	3	235	88.7	30	11.3	220	83.1	17	6.5	28	10.6
UMCU Utrecht	581	6.5	539	92.8	42	7.2	516	88.9	30	5.2	35	6.1
VUMC Amsterdam	236	2.7	204	86.4	32	13.6	178	75.5	30	12.8	28	11.9
EMC Rotterdam	1019	11.4	960	94.2	59	5.8	852	83.7	120	11.8	47	4.7
St. Elisabeth Ziekenhuis Tilburg	410	4.6	397	96.8	13	3.2	371	90.5	30	7.4	9	2.2
Kennemer Gasthuis/EG Haarlem	167	1.9	147	88.0	20	12.0	125	74.9	23	13.8	19	11.4
MCA Alkmaar	79	0.9	74	93.7	5	6.3	70	88.7	6	7.6	3	3.8
MST Enschede	192	2.2	170	88.5	22	11.5	166	86.5	7	3.7	19	9.9
OLVG Oosterpark Amsterdam	926	10.3	848	91.6	78	8.4	798	86.2	65	7.1	63	6.9
Slotervaart Amsterdam	611	6.8	554	90.7	57	9.3	509	83.4	58	9.5	44	7.3
MCH locatie Westeinde Den Haag	301	3.4	282	93.7	19	6.3	265	88.1	23	7.7	13	4.4
Leyenburg Den Haag	337	3.8	317	94.1	20	5.9	281	83.4	38	11.3	18	5.4
Ziekenhuis Rijnstate Arnhem	245	2.8	221	90.2	24	9.8	213	87	11	4.5	21	8.6
OLVG Prinsengracht Amsterdam	396	4.5	360	90.9	36	9.1	334	84.4	29	7.4	33	8.4
MCL Leeuwarden	101	1.2	97	96.0	4	4.0	92	91.1	6	6	3	3
Ziekenhuis Walcheren Vlissingen	62	0.7	57	91.9	5	8.1	51	82.3	6	9.7	5	8.1
OLVG locatie JvG Amsterdam	265	3	252	95.1	13	4.9	245	92.5	12	4.6	8	3.1
Catharina Eindhoven	145	1.7	143	98.6	2	1.4	131	90.4	14	9.7	0	0
Isala Klinieken/Sophia Zwolle	100	1.2	97	97.0	3	3.0	95	95	3	3	2	2
St. Lucas Andreas Amsterdam	66	0.8	61	92.4	5	7.6	61	92.5	3	4.6	2	3.1
Totaal	**8999**	**100**	**8317**	**92.5**	**682**	**7.6**	**7752**	**86.2**	**679**	**7.6**	**568**	**6.4**

Tabel 1: Aantal per 31 december 2003 geregistreerde volwassen patiënten waarvan gegevens zijn verzameld door de SHM

HIV-Behandelcentrum	In 2003 geïncludeerd		In 2003 geïncludeerd; dood		In 2003 geïncludeerd; AIDS		In 2003 geïncludeerd; follow-up		In 2003 geïncludeerd; geen follow-up		In 2003 geïncludeerd; geen follow-up en dood	
	N	%	N	%	N	%	N	%	N	%	N	%
AMC Amsterdam	244	16.6	5	2.0	57	23.4	243	99.6	1	0.5	0	0
AZG Groningen	71	4.9	4	5.6	16	22.5	68	95.8	2	2.9	1	1.5
LUMC Leiden	38	2.6	1	2.6	13	34.2	37	97.4	1	2.7	0	0
AZM Maastricht	27	1.9	0	0.0	2	7.4	22	81.5	5	18.6	0	0
UMC St. Radboud Nijmegen	41	2.8	3	7.3	18	43.9	38	92.7	2	4.9	1	2.5
UMCU Utrecht	75	5.1	1	1.3	14	18.7	71	94.7	4	5.4	0	0
VUMC Amsterdam	35	2.4	0	0.0	7	20.0	28	80	7	20	0	0
EMC Rotterdam	191	13	3	1.6	26	13.6	124	65	67	35.1	0	0
St. Elisabeth Ziekenhuis Tilburg	35	2.4	0	0.0	3	8.6	34	97.2	1	2.9	0	0
Kennemer Gasthuis/EG Haarlem	22	1.5	1	4.5	4	18.2	22	100	0	0	0	0
MCA Alkmaar	16	1.1	0	0.0	2	12.5	16	100	0	0	0	0
MST Enschede	48	3.3	1	2.1	9	18.8	44	91.7	4	8.4	0	0
OLVG Oosterpark Amsterdam	255	17.3	9	3.5	64	25.1	220	86.3	32	12.6	3	1.2
Slotervaart Amsterdam	62	4.2	0	0.0	9	14.5	59	95.2	3	4.9	0	0
MCH locatie Westeinde Den Haag	43	3	0	0.0	3	7.0	41	95.4	2	4.7	0	0
Leyenburg Den Haag	46	3.2	1	2.2	11	23.9	37	80.5	9	19.6	0	0
Ziekenhuis Rijnstate Arnhem	33	2.3	2	6.1	4	12.1	33	100	0	0	0	0
OLVG Prinsengracht Amsterdam	43	3	0	0.0	2	4.7	39	90.7	4	9.4	0	0
MCL Leeuwarden	22	1.5	1	4.5	1	4.5	22	100	0	0	0	0
Ziekenhuis Walcheren Vlissingen	6	0.5	0	0.0	1	16.7	5	83.4	1	16.7	0	0
OLVG locatie JvG Amsterdam	22	1.5	0	0.0	4	18.2	21	95.5	1	4.6	0	0
Catharina Eindhoven	43	3	2	4.7	4	9.3	38	88.4	5	11.7	0	0
Isala Klinieken/Sophia Zwolle	39	2.7	0	0.0	4	10.3	39	100	0	0	0	0
St. Lucas Andreas Amsterdam	21	1.5	2	9.5	6	28.6	20	95.3	1	4.8	0	0
Totaal	**1478**	**101**	**36**	**2.5**	**284**	**19.3**	**1321**	**89.4**	**152**	**10.3**	**5**	**0.4**

Tabel 2: Aantal in 2003 geregistreerde patiënten waarvan gegevens zijn verzameld door de SHM

In totaal 168 patiënten hebben bezwaar aangetekend tegen registratie en verzameling van hun gegevens in de SHM database. Het overzicht per HIV-Behandelcentrum is weergegeven in Tabel 3. Het gebruik van een informed consent procedure in plaats van een geen bezwaar procedure verklaart grotendeels de verschillen tussen de ziekenhuizen.

Registratie van aan HIV blootgestelde en met HIV geïnfecteerde kinderen

In totaal zijn nu 77 kinderen geregistreerd met een HIV-infectie. Daarvan is 1 patiënt overleden. De mediane leeftijd in 2003 was 8 jaar (IQR 5-12 jaar). In 2003 zijn 58 van de 76 kinderen jonger dan twaalf jaar; 32 hiervan zijn jongens en 26 meisjes. Zij zijn alle nog in leven. Bijna 65% van de kinderen heeft Nederland als land van herkomst en 27% is afkomstig uit Zuidelijk Afrika. Tabel 4 geeft een overzicht van de geïncludeerde kinderen per HIV-Behandelcentrum.

De registratie en verzameling van de gegevens van kinderen is nog steeds niet voldoende op gang gekomen. Het overleg met de betrokken kinderartsen over de implementatie van invoerschermen voor met HIV geïnfecteerde of aan HIV blootgestelde kinderen heeft aanmerkelijk meer tijd gekost dan voorzien. Deze schermen worden thans gebouwd; een aantal HIV-Behandelcentra is inmiddels wel begonnen met de registratie van kinderen.

Bezwaar tegen inclusie in monitoring	t/m 31-12-2003		in 2003	
HIV-Behandelcentrum	**N**	**%**	**N**	**%**
AMC Amsterdam	8	4.8	4	3.9
AZG Groningen	5	3	1	1
LUMC Leiden	7	4.2	2	2
AZM Maastricht	3	1.8	1	1
UMC St. Radboud Nijmegen	4	2.4	2	2
UMCU Utrecht	25	14.9	8	7.7
VUMC Amsterdam	1	0.6	1	1
EMC Rotterdam	9	5.4	3	2.9
St. Elisabeth Ziekenhuis Tilburg	0	0	1	1
Kennemer Gasthuis/EG Haarlem	1	0.6	0	0
MCA Alkmaar	0	0	0	0
MST Enschede	2	1.2	3	2.9
OLVG Oosterpark Amsterdam	62	37	62	59.1
Slotervaart Amsterdam	6	3.6	1	1
MCH Westeinde Den Haag	12	7.2	5	4.8
Leyenburg Den Haag	19	11.4	7	6.7
Ziekenhuis Rijnstate Arnhem	2	1.2	0	0
OLVG Prinsengracht Amsterdam	0	0	1	1
MCL Leeuwarden	0	0	0	0
Ziekenhuis Walcheren Vlissingen	0	0	0	0
OLVG JvG Amsterdam	0	0	0	0
Catharina Ziekenhuis Eindhoven	0	0	1	1
Isala Klinieken Sophia Zwolle	1	0.6	2	2
St. Lucas Andreas Amsterdam	1	0.6	0	0
Totaal	**168**		**105**	

Tabel 3: Aantallen patiënten die bezwaar maken tegen inclusie van hun gegevens in de SHM monitoring database

Ziekenhuis	N	% van totaal
Emma Kinderziekenhuis AMC Amsterdam	27	35.07
AZG Groningen	1	1.3
LUMC Leiden	4	5.2
AZM Maastricht	2	2.6
Wilhelmina Kinderziekenhuis UMCU Utrecht	35	45.46
Sophia Kinderziekenhuis EMC Rotterdam	3	3.9
St. Elisabeth Tilburg	2	2.6
Slotervaart Ziekenhuis Amsterdam	1	1.3
Catharina Ziekenhuis Eindhoven	2	2.6
Totaal	**77**	

Tabel 4: Aantal geregistreerde kinderen met een HIV-infectie of blootstelling aan HIV

Registratie HIV-geïnfecteerde zwangeren

In totaal is bij 438 HIV-geïnfecteerde vrouwen een zwangerschap geregistreerd (Tabel 5). Bij 75.3% van deze vrouwen betrof het een eerste zwangerschap. Bij 19.2% gaat het om vrouwen die twee keer zwanger zijn geweest en bij de resterende 4.5% om vrouwen die meer dan twee keer zwanger waren. In 2003 werden 77 HIV-geïnfecteerde zwangeren geregistreerd, waarvan bij 49 (63.6%) de HIV-diagnose voor de zwangerschap, en bij 28 (36.4%) tijdens de zwangerschap werd gesteld. Van de zwangere vrouwen met HIV in 2003 is 75.3% afkomstig uit een ander land dan Nederland en 58.4% uit Zuidelijk Afrika. Meer dan de helft (53.3%) van de zwangere vrouwen met HIV wordt in 2003 al met HAART behandeld voor de zwangerschap; 36.4% start pas met behandeling tijdens de zwangerschap. De zwangerschapsduur in deze groep (2003) is bij 11.7% korter dan 26 weken en eveneens 11.7% langer. In 75.3% van de vrouwen is het einde van de zwangerschap (nog) niet geregistreerd.

In aansluiting op de registratie van kinderen worden data-invoerschermen aangepast om de registratie en monitoring van zwangeren te verbeteren.

Ziekenhuis	N	% t/m 2003	N	% in 2003
AMC Amsterdam	128	29.23	23	29.88
AZG Groningen	31	7.08	4	5.2
LUMC Leiden	20	4.57	5	6.5
AZM Maastricht	6	1.37	0	0
UMC St. Radboud Nijmegen	18	4.11	4	5.2
UMCU Utrecht	40	9.14	7	9.1
VUMC Amsterdam	1	0.23	0	0
EMC Rotterdam	73	16.67	6	7.8
St. Elisabeth Ziekenhuis Tilburg	19	4.34	2	2.6
Kennemer Gasthuis Haarlem	9	2.06	5	6.5
MCA Alkmaar	5	1.15	1	1.3
MST Enschede	4	0.92	3	3.9
OLVG Oosterpark Amsterdam	18	4.11	1	1.3
Slotervaart Amsterdam	3	0.69	1	1.3
MCH Westeinde Den Haag	7	1.6	2	2.6
Leyenburg Den Haag	23	5.26	4	5.2
Rijnstate Arnhem	10	2.29	2	2.6
OLVG Prinsengracht Amsterdam	2	0.46	0	0
MCL Leeuwarden	3	0.69	1	1.3
Ziekenhuis Walcheren Vlissingen	1	0.23	0	0
OLVG JvG Amsterdam	2	0.46	1	1.3
Catharina Eindhoven	11	2.52	4	5.2
Isala Klinieken Sophia Zwolle	4	0.92	1	1.3
St. Lucas Andreas Amsterdam	0	0	0	0
Totaal	**438**	**100.1**	**77**	**100.08**

Tabel 5: Geregistreerde HIV-geïnfecteerde zwangeren per HIV-Behandelcentrum totaal (t/m 31-12-2003) en in 2003

Monitoring van HIV-geïnfecteerde volwassenen

Bij 97.5% van de bij de SHM geregistreerde HIV-geïnfecteerde patiënten betreft het een infectie met het type 1. Van 0.3% is een type 2 infectie geregistreerd; van de overige 2.2% is niet bekend of sprake is van een type 1, type 2 of type 1 en 2 infectie [1]. Van de per eind december 2003 in de registratie en monitoring geïncludeerde patiënten is 78% man en 22% vrouw.

De mediane follow-up duur is 5.4 jaar (IQR 2.3-9.2); 5.6 (2.6-9.6) jaar voor de mannen en 4.0 (1.7-7.9) voor de vrouwen. De mediane leeftijd voor het gehele cohort bedroeg 34 jaar (28-41). HIV-geïnfecteerde vrouwen zijn op het moment van de HIV-diagnose mediaan 6 jaar jonger dan mannen. Het aantal nieuwe HIV-diagnoses per jaar neemt geleidelijk toe van 246 in 1990 tot 878 in 2002. Het aandeel vrouwen in de met HIV geïnfecteerde populatie neemt eveneens geleidelijk toe en was in 2003 gestegen tot 30.5%.

De samenstelling van de HIV-geïnfecteerde populatie in Nederland die door de SHM wordt geregistreerd is aan verandering onderhevig. Een meerderheid van de patiënten is van het mannelijk geslacht en is geïnfecteerd via homoseksueel contact. De relatieve bijdrage van deze groep aan de nieuw gediagnostiseerde infecties neemt echter af; het duidelijkst is deze ontwikkeling in de groep mannen met homoseksuele contacten die jonger zijn dan 30 jaar. Daarentegen neemt het aantal nieuwe infecties onder homoseksuele mannen boven 30 jaar juist licht toe.

Bij heteroseksuele transmissie wordt een heel ander beeld zichtbaar. Hier is sprake van een continu dalend aandeel van autochtone patiënten (patiënten met Nederland als geboorteland) en een vrijwel omgekeerd evenredig stijgend aandeel van patiënten afkomstig uit Zuidelijk Afrika. Deze trend wordt ook waargenomen in de rest van West-Europa. In de groep afkomstig uit Zuidelijk Afrika is het aandeel vrouwen met een HIV-infectie groter dan het relatieve aandeel mannen.

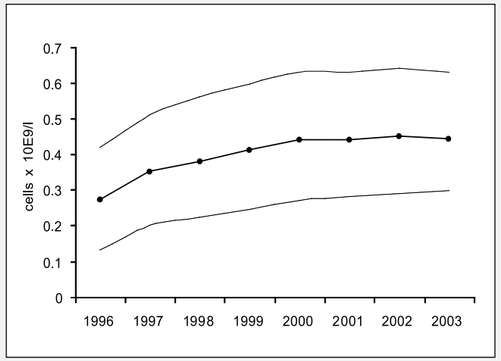
De frequentie van bezoeken aan de behandelend internist neemt sinds 1999 gestadig af van gemiddeld 4.8 (SD 2.2) per jaar tot 3 (1.9) in 2003 (Tabel 6). Dit cijfer voor 2003 kan nog veranderen, aangezien er bij een aantal instellingen een achterstand bestaat van meer dan een half jaar. Desalniettemin is een trend waarneembaar, waarbij - bij een vrijwel gelijkblijvend aantal arts-behandelaars - het aantal patiënten in follow-up is

toegenomen en als gevolg daarvan de bezoekfrequentie bij de HIV-Behandelaars afneemt. In verscheidene HIV-Behandelcentra wordt een deel van de patiëntbezoeken uitgevoerd door de AIDS-consulent. Deze bezoeken zullen in de toekomst ook door de SHM worden geregistreerd.

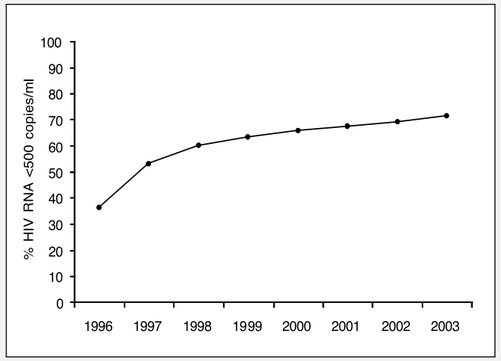
Het aantal metingen per jaar neem eveneens af. In 1999 werd gemiddeld 3.9 (1.8) keer het CD4 cel aantal in perifeer bloed gemeten en in 2003 2.6 (1.7) keer. Voor de bepaling van de HIV-RNA spiegels waren deze getallen 3.7 (2) en 2.6 (1.6). De gevolgen van deze veranderingen in de kostenontwikkeling van de behandeling van HIV-geïnfecteerden zijn weergegeven in het hoofdstuk 'Changing direct costs of HIV treatment since the introduction of HAART in the Netherlands' op pagina 52 van dit jaarverslag.

	Gemiddelde bezoekfrequentie (±SD)									
HIV-Behandelcentrum	**1999**		**2000**		**2001**		**2002**		**2003**	
AMC Amsterdam	5.3	(2.4)	4.7	(2.2)	4.6	(2.6)	4.1	(2.3)	3.7	(2.1)
AZG Groningen	6.4	(3)	4.9	(2.3)	5	(2.5)	4.9	(2.5)	4.1	(2.3)
LUMC Leiden	5.3	(2.3)	4.6	(2.4)	4.2	(2.5)	3.5	(2)	3.5	(1.8)
AZM Maastricht	4.4	(1.8)	4.6	(2)	4.7	(2.5)	4.1	(2.2)	2.6	(2)
UMC St. Radboud Nijmegen	6.1	(3.3)	5.1	(2.7)	5.5	(3.5)	5.3	(3.6)	4.3	(2.6)
UMCU Utrecht	4.3	(2.4)	4.3	(2)	4.1	(2.4)	3.6	(1.9)	2.8	(1.9)
VUMC Amsterdam	5.8	(2.5)	5	(2.6)	4.3	(2)	4	(1.7)	3	(2.6)
EMC Rotterdam	4.4	(1.4)	4	(1.5)	3.5	(1.6)	3	(1.5)	2.4	(1.4)
St. Elisabeth Ziekenhuis Tilburg	3.6	(1)	3.2	(1.1)	3.3	(1.2)	3.1	(1.4)	2.9	(1.3)
Kennemer Gasthuis/EG Haarlem	5.8	(3)	4.8	(2.3)	4.5	(2.6)	3.8	(2)	2.4	(2.2)
MCA Alkmaar	3.4	(1.3)	3.5	(1.3)	3.5	(2)	3.1	(1.4)	1.8	(1)
MST Enschede	6	(3.3)	5.1	(2.7)	5.5	(2.6)	5.4	(2.8)	5.2	(2.4)
OLVG locatie Oosterpark	4.3	(1.9)	4.1	(1.9)	3.6	(1.8)	3.2	(1.5)	2.4	(1.5)
Slotervaart Amsterdam	3.9	(1.6)	3.3	(1.5)	3	(1.6)	3.1	(1.6)	2.5	(1.5)
MCH Westeinde Den Haag	4.8	(2.2)	4	(2)	3.9	(2)	3	(1.4)	2.1	(1.4)
Leyenburg Ziekenhuis Den Haag	4.6	(1.4)	4.1	(1.8)	3.7	(1.6)	3.3	(1.5)	3.2	(1.8)
Ziekenhuis Rijnstate Arnhem	5	(1.8)	4.6	(1.7)	4.6	(1.9)	3.8	(1.8)	3.5	(1.7)
OLVG Prinsengracht Amsterdam	4.8	(2.2)	4.3	(2.3)	3.8	(1.7)	3.5	(1.9)	3	(1.7)
MCL Leeuwarden	3.9	(1.5)	3.8	(0.8)	4.3	(2.2)	3.8	(1.3)	3.1	(1.6)
Ziekenhuis Walcheren Vlissingen	4.8	(1.6)	4	(2.3)	4.2	(2.2)	4.7	(2.3)	2.5	(1.9)
OLVG locatie JvG Amsterdam	7	(1.4)	4	(1.8)	3.8	(1.4)	3.4	(1.8)	2.4	(1.2)
Catharina Ziekenhuis Eindhoven	3.7	(1.2)	3.9	(1.9)	3.3	(1.6)	4.2	(2)	4.3	(1.9)
Isala Klinieken/Sophia Zwolle	4.8	(1.5)	4.2	(2.2)	4.1	(2.4)	4.4	(1.4)	3.7	(2)
St. Lucas Andreas Amsterdam					3.8	(1.9)				
Totaal	**4.8**	**(2.2)**	**4.2**	**(2.1)**	**4**	**(2.2)**	**3.7**	**(2.1)**	**3**	**(1.9)**

Tabel 6: Frequentie per jaar van de spreekuurbezoeken bij de behandelend arts



Figuur 1: Toename van het gemiddelde aantal CD4+ T cellen in perifeer bloed in de gehele populatie HIV-geïnfecteerden na introductie van HAART in 1996

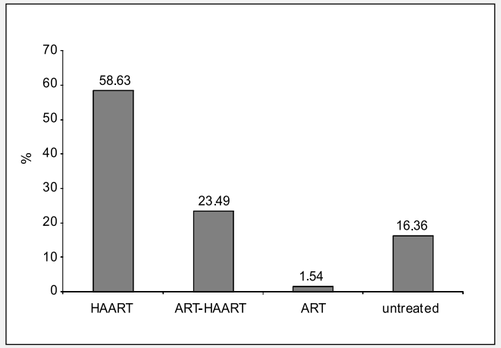


Figuur 2: Toename van het percentage patiënten met HIV-RNA spiegels <500 kopieën/ml bloed in de gehele populatie na introductie van HAART in 1996

In de totale geregistreerde populatie stijgt het aantal CD4+ T cellen met gemiddeld 120 cellen per mm^3 sinds 1996 tot 2003 (Figuur 1), terwijl het percentage patiënten waarbij de concentratie HIV-RNA in plasma daalt ≤500 copieen/ml toeneemt van 36.2 in 1996 tot 71.4 in 2003 (Figuur 2).

Initieel HAART regiem	**2002 %**	**2003 %**
AZT 3TC LOP/r	19.8	19.8
AZT 3TC NVP	14.1	15.3
AZT 3TC EFV	13.4	12.1
AZT 3TC ABC	10.7	7.9
AZT 3TC NFV	5.6	5.3
AZT 3TC ABC LOP/r	5.5	7.2
d4T 3TC LOP/r	3.7	1.2
AZT ddI IDV	3	2.8
TDF 3TC EFV	2.2	8.8
TDF 3TC NVP	2.2	3.7
AZT 3TC ABC EFV	1.8	2.8
d4T 3TC NVP	1.4	0.9
AZT 3TC KAL EFV	1.4	2.3
TDF ddI EFV	0.1	1.6
	84.9	91.7

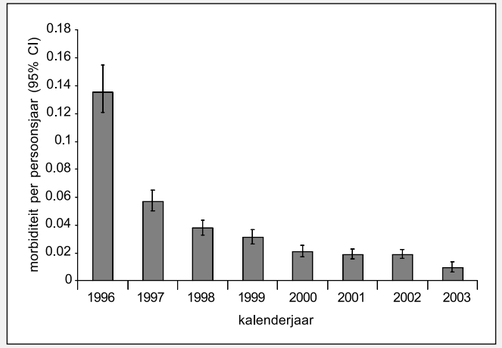
Tabel 7: Meest gebruikte combinaties in de behandeling met HAART in 2002 en 2003



Figuur 3: Percentuele aandeel in 2003 van naive en voorbehandelde patienten dat wordt behandeld met HAART, met non-HAART en dat niet wordt behandeld

Van de totale populatie die in 2003 nog in follow-up is wordt 82.1% behandeld met Highly Active Antiretroviral Therapy (HAART); 23.5% is voorbehandeld met een non-HAART combinatie van antiretrovirale middelen.

Slechts 1.5% van de patiënten wordt in 2003 nog steeds behandeld met een non-HAART combinatie, terwijl 16.4% helemaal niet wordt behandeld (Figuur 3). De meest populaire combinaties van middelen is opgenomen in Tabel 7. AZT+3TC als backbone in de HAART combinatie wordt gebruikt bij 75% van de behandelde patiënten. Lopinavir + ritonavir wordt in 19% toegevoegd. Het gebruik van nevirapine en efavirenz blijft stabiel tussen de 12% en 14% gedurende 2002 en 2003. Zichtbaar wordt het gebruik van tenofovir.

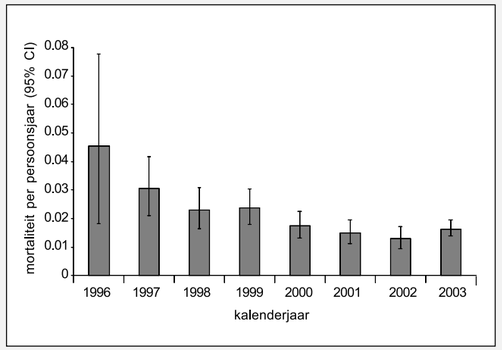


Figuur 4: Morbiditeit per jaar

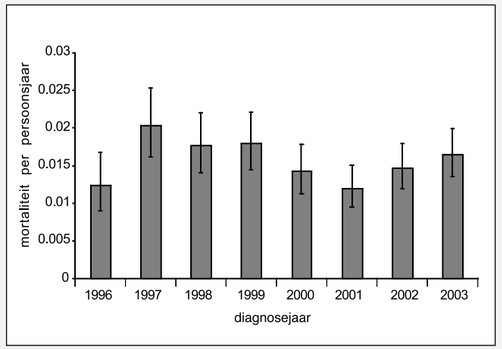
De morbiditeit (Figuur 4) onder de met HAART behandelde patiënten blijft sinds de introductie in 1996 dalen en komt in 2003 op 0.01 per persoonsjaar. De mortaliteit in 2003 is 0.02 per persoonsjaar en lijkt ten opzichte van 2002 niet verder af te nemen (Figuur 5). De mortaliteit per HIV-diagnosejaar neemt zelfs iets toe, van 0.01 in 2001 tot 0.02 per persoonsjaar in 2002 en 2003, hetgeen er mogelijk op wijst dat patiënten in de laatste jaren pas in een latere fase van de infectie worden gediagnostiseerd (Figuur 6).

Verslag SHM registratieprogramma

Als vervolg op een eerdere studie naar veranderingen in de mortaliteit en morbiditeit sinds de introductie van HAART [2] werd in samenwerking met het Verbond van



Figuur 5: Mortaliteit per kalenderjaar



Figuur 6: Mortaliteit per diagnosejaar

Verzekeraars de studie afgerond naar de veranderingen in de mortaliteit onder HIV-geïnfecteerde patiënten. Mortaliteitratio's van behandelde HIV-geïnfecteerde patiënten werden vergeleken met die van op leeftijd en geslacht gematchte niet-geïnfecteerde Nederlandse bevolking; prognostische survivalmodellen werden ontwikkeld voor het initiële effect van HAART. Een hoog CD4 cel aantal na 24 weken HAART-behandeling en het beginnen van de behandeling met HAART na 1998 bleken sterk geassocieerd te zijn met een hogere 5-jaars overlevingskans. Bovendien bleken de mortaliteitratio's van met HAART behandelde HIV-geïnfecteerde patiënten met een goede immunologische respons vergelijkbaar met die van de niet-geïnfecteerde Nederlandse bevolking.

Onder 1.156 therapie-naïeve patiënten werd onderzoek gedaan naar het effect van tijdelijke onderbreking van HAART, een verschijnsel dat bij relatief veel patiënten wordt geregistreerd. Na mediaan 9.1 (IQR 2.1-25.1) maanden HAART behandeling volgde een therapie-interruptie van 3.5 (IQR 1.1-13) maanden. Iets minder dan de helft van de patiënten had voor de interruptie een plasma HIV-RNA concentratie <500 kopieën per ml bereikt. Op het moment van reïnititatie van HAART was bij de overgrote meerderheid van de patiënten de HIV-RNA concentratie weer gestegen tot waarden >500 kopieën/ml (mediaan load 4.8log kopieën/ml). Een jaar na reïnitiatie van HAART bereikt 77% van de patiënten weer een HIV-RNA waarde <500. Het bleek dat de HAART behandeling na het hervatten van de therapie minder effectief was dan daarvoor, en afhankelijk van de immunologische en virologische conditie die voor en tijdens de interruptie was bereikt.

Het lange termijn effect van verschillende regiems werd bestudeerd in een subgroep van 849 therapie-naïeve patiënten die werden behandeld met een HAART combinatie bestaande uit een d4T+3TC of AZT+3TC backbone in combinatie met een NNRTI of een of twee PI's, dan wel de NRTI abacavir. De CD4 cel slope tussen 18 en 96 weken behandeling werden vergeleken met behulp van mixed effect modellen. Geen verschil werd gevonden tussen de twee NRTI backbones. Voorlopige resultaten wijzen op een hogere slope dan werd voorspeld in de patiënten die een CD4 cel aantal van 200/mm^3 hadden na de eerste 18 weken behandeling en die werden behandeld met een combinatie met nelfinavir, saquinavir+ritonavir of indinavir+ritonavir in vergelijking tot combinaties met abacavir, nevirapine en lopinavir+ritonavir. De lopinavir+ritonavir groep bleek echter klinisch slechter bij de start van de HAART behandeling dan de andere groepen.

	N sequenties	
Virologisch laboratorium	**ATHENA**	**SHM**
EMC Rotterdam	81	88
UMCU Utrecht	263	900*
LUMC Leiden	65	140
AMC Amsterdam	375	710
Totaal	**784**	**1838**

Tabel 8: Aantal sequenties verzameld tot en met 2003 en opgenomen in de SHM sequentie database

*Bij benadering; de sequenties aangeleverd door UMCU Utrecht zijn nog in administratieve bewerking

Onderzoek aan de hand van de ultimo 2003 beschikbare HIV RT en protease sequenties liet zien dat in 6% van de nieuwe infecties in Nederland virus wordt overgedragen met mutaties die resistentie veroorzaken. Door beperkingen in dit onderzoek – met name de onvoldoende beschikbaarheid van resistentiegegevens - kan sprake zijn van een onderschatting van de resistentie-transmissieratio. Begin 2004 zijn de resistentiegegevens van grote aantallen patiënten in het SHM resistentie-databestand opgenomen (zie Tabel 8).

Toxiciteit in combinatie met het virologisch en immunologisch effect van frequent gebruikte HAART combinaties werd vergeleken in een groep van 3.524 therapie-naïeve patiënten. Combinaties met d4T+3TC als backbone werden significant vaker gestopt als gevolg van toxiciteit dan die met AZT+3TC; tussen deze twee backbones bleek geen verschil in tijd tot virologisch en immunologisch effect. Combinaties met efavirenz en nevirapine waren virologisch het meest effectief in vergelijking met abacavir, nelfinavir of

lopinavir+ritonavir. De HAART-combinatie met lopinavir +ritonavir was daarentegen immunologisch het meest succesvol. De backbone AZT+3TC, gecombineerd met abacavir, nelfinavir, lopinavir+ritonavir, nevirapine of efavirenz, bleek minder toxisch dan andere combinaties. Dit onderzoek zal verder worden voortgezet; in de toekomst zal met name worden gekeken naar de meer recent geïntroduceerde initiële HAART-combinaties.

Nationale samenwerking

RIVM (Dr. M. van der Laar)
Aan het RIVM worden gegevens verstrekt in verband met de registratie van nieuwe HIV-infecties als onderdeel van het nationale HIV-registratie en surveillance programma dat door het RIVM wordt gecoördineerd [3].

De Amsterdamse cohort studies (Prof. Dr. R.A. Coutinho, GG&GD, Prof. Dr. F. Miedema, CLB-Sanquin; Prof. Dr. B. Berkhout, afdeling Humane Retrovirologie, AMC; Prof. Dr. J.M.A. Lange, afdeling Inwendige Geneeskunde, AMC)
De SHM verzorgt de verzameling van klinische follow-up gegevens van vooral de deelnemers aan de cohortstudie onder mannen met homoseksuele contacten.

Verbond van Verzekeraars
De samenwerking met de werkgroep HIV/AIDS van de Nederlandse Bond van Verzekeraars (Den Haag) concentreert zich op de modelmatige benadering van het vraagstuk of de kans op overleven sinds de introductie van HAART is toegenomen en of dat aanleiding is om het actuariële model voor het verstrekken van levensverzekeringen aan met HIV geïnfecteerde personen zou kunnen worden aangepast. De samenwerking startte in 2002, werd in 2003 voortgezet en zal - op dit onderdeel - begin 2004 worden afgerond.

Internationale samenwerking

DIDE: Department of Infectious Disease Epidemiology (DIDE), Faculty of Medicine, Imperial College, Londen, UK (Prof. Dr. Roy Anderson). Tussen DIDE en SHM bestaat sinds 2002 een wetenschappelijke samenwerkingsovereenkomst die is gericht op statistische en mathematische ondersteuning van DIDE aan SHM bij de analyse van observationele cohortdata enerzijds en de uitvoering van het HIV registratieprogramma anderzijds.

Een belangrijk doel van het DIDE onderzoeksprogramma is het verkrijgen van meer inzicht in het samenspel van variabelen die het typische beloop van een infectie in een individuele gastheer, alsmede de variabelen die het beloop van een infectie in een bevolkingsgroep bepalen. Voor het beantwoorden van dergelijke onderzoeksvragen zijn technieken nodig zoals de bestudering van de eigenschappen van non-lineaire differentiaalvergelijkingen, de organisatie en het management van grootschalige veldstudies naar transmissie en beheersing van een infectie in bevolkingsgroepen en de bewerking en analyse van grote datasets.

In het kader van deze samenwerking werd een begin gemaakt met onderzoek naar veranderingen in de therapietrouw bij de chronische behandeling van de HIV-infectie en het effect hiervan op het ontwikkelen van resistentie. Dit onderzoek wordt uitgevoerd samen met de afdelingen Inwendige Geneeskunde (Dr. J.M. Prins en Prof. Dr. J.M.A. Lange) en Humane Retrovirologie (Dr. S. Jurriaans) van het AMC bij de Universiteit van Amsterdam, de afdeling Medische Psychologie (Prof. Dr. G.J. Kok) van de Universiteit van Maastricht en de Klinisch Farmacologische afdelingen van het Universitair Medisch Centrum Nijmegen, St. Radboud (Dr. D.M. Burger) en van het Slotervaart Ziekenhuis Amsterdam (Prof. Dr. J.H. Beijnen).

ART: De Antiretroviral Therapy (ART) Cohort Collaboration (gecoördineerd door Prof. Matthias Egger, Department of Social and Preventive Medicine, University of Bern, Switzerland) is een internationale samenwerking tussen (op dit moment) 13 cohort studies uit Europa en Noord-Amerika. ART werd begonnen om de prognose te kunnen schatten van therapie-naïeve patiënten die met HAART begonnen. In Tabel 9 zijn de cohorten opgenomen die per oktober 2002 onderdeel zijn van deze samenwerking. Van de zijde van de SHM is Dr. Frank de Wolf de principal investigator voor deze samenwerking.

Cohort	Country
French Hospital Database on HIV (FHDH)	France
Italian Cohort of Antiretroviral-Naive Patients (ICONA)	Italy
Swiss HIV Cohort Study (SHCS)	Switzerland
AIDS Therapy Evaluation project Netherlands (ATHENA)	The Netherlands
EuroSIDA	20 in Europe
Collaborations in HIV Outcomes Research US (CHORUS)	USA
Frankfurt HIV Cohort	Germany
Antiprotease Cohort (APROCO)	France
Aquitaine Cohort	France
British Columbia Centre for Excellence in HIV/AIDS	Canada
Royal Free Hospital Cohort	UK
South Alberta Clinic	Canada
Köln/Bonn Cohort	Germany

Tabel 9: Cohort studies die in de ART Cohort Collaboration participeren

Een vervolgstudie op de eerste resultaten [4] uit deze samenwerking werd eveneens gepubliceerd in de Lancet [5]. Deze studie laat zien dat het resultaat dat wordt bereikt gedurende de eerste 24 weken van behandeling met HAART bepalend is voor de uitkomst van die behandeling.

DAD: Deze samenwerking tussen een aantal observationele klinische cohorten richt zich op de vroege herkenning van cardiovasculaire problemen die het gevolg zouden kunnen zijn van de behandeling van HIV met antiretrovirale middelen en dan met name HIV proteaseremmers. Dr. DJ Lundgren (Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, Denmark) coördineert deze studie; Dr. Peter Reiss (afdeling Inwendige Geneeskunde, AMC, Amsterdam) is de principal investigator voor ATHENA/SHM bij deze studie. De SHM heeft in 2003 de uitvoeringsverantwoordelijkheid voor DAD overgenomen. De eerste resultaten van de DAD studie zijn in 2003 gepubliceerd en laten een significante relatie zien tussen het ontwikkelen van cardiovasculaire problemen en het gebruik van proteaseremmers [6].

PLATO (Pursuing Later Treatment Options): Het aantal patiënten, waarbij de behandeling met HAART combinaties van antiretrovirale middelen van alle drie de klassen faalt, neemt toe. Van deze groep patiënten is de prognose en de factoren die geassocieerd zijn met klinische progressie nog onvoldoende beschreven. Bij deze patiënten kan meestal geen onderdrukking van de vermenigvuldiging van HIV tot waarden beneden de detectiegrens van de tests meer worden bereikt. Doel van de behandeling van deze patiënten wordt dan vaak om het aantal CD4+ T cellen op peil te houden en zo het risico voor ziekteprogressie te verminderen. De PLATO samenwerking is ontwikkeld binnen de ART cohort samenwerking en omvat dus dezelfde 13 observationele cohorten in Europa en Noord-Amerika. Gegevens over ziekteprogressie bij patiënten na drie-klassen virologisch falen worden verzameld. Dr. Bruno Ledergerber (Division of Infectious Diseases, University Hospital Zurich, Switzerland) coördineert de studie en Dr. Peter Reiss (afdeling Inwendige Geneeskunde, AMC, Amsterdam) is principal investigator voor ATHENA/SHM bij deze studie.

Het doel van deze studie is de voorspellende waarde van de aantallen CD4 cellen en virale load voor mortaliteit in deze patiënten te kunnen schatten en een

analyse te doen naar voorspellers voor veranderingen in CD4 cel aantallen gedurende de follow-up. De resultaten wijzen op een aanmerkelijke mortaliteit onder patiënten met virologisch falen nadat zij met middelen uit elk van de drie klassen zijn behandeld. Bovendien blijkt dat mortaliteit is geassocieerd met lage CD4 cel aantallen. Patiënten die op antivirale therapie blijven, waarbij de virale load, hoewel meetbaar, beneden waarden van 4log kopieën/ml plasma blijven en een 1-2log reductie weten te bereiken ten opzichte van de start van HAART blijken een goede kans te hebben om immunologische verslechtering te vermijden.

Referenties

1. Gras L, Van Sighem AI, Van Valkengoed I, Zaheri S, De Wolf F, on behalf of the Netherlands collaborative HIV treatment centres. Monitoring of human immunodeficiency virus (HIV) infection in the Netherlands (2003). HIV Monitoring Foundation, Amsterdam, The Netherlands; 2003 Dec 1. Report No.: 2.

2. Van Sighem AI, Van De Wiel MA, Ghani AC, Jambroes M, Reiss P, Gyssens IC, et al. Mortality and progression to AIDS after starting highly active antiretroviral therapy. AIDS 2003 Oct 17;17(15):2227-36.

3. Op de Coul EL, Van Valkengoed I, Van Sighem AI, De Wolf F, Van der Laar MJW. HIV en AIDS in Nederland. Rijksinstituut voor Volksgezondheid en Milieu; 2003 Dec 1. Report No.: 441100018/2003.

4. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002 Jul 13;360(9327):119-29.

5. Egger M, Chene G, Sterne JA, May M, Costagliola D, Ledergerber B, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet 2003 Aug 30;362(9385):679-86.

6. Friis-Moller N, Sabin CA, Weber R, D'Arminio MA, El Sadr WM, Reiss P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 2003 Nov 20;349(21):1993-2003.

English

HMF

The HIV Monitoring Foundation (HMF) was founded on November 11, 2001 and became operational on May 1, 2002. The HMF is based in Amsterdam (Chamber of Commerce # 34160453). The Dutch Minister of Health has appointed the HMF as the executive organisation for the registration and monitoring of HIV infected patients in follow-up in the Dutch Treatment Centres.

The mission of the HMF is to further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection. In order to achieve this mission, the HMF engages in the following activities:

- Collection and maintenance of anonymous data obtained from HIV infected patients and of their antiretroviral treatment;
- processing of data for the benefit of reporting to government and other organisations on the course and treatment of HIV infection;
- making data available to HIV infected individuals and their treating physicians;
- providing data for the benefit of scientific research and for consensus formation;
- making data available to the media and other interested parties for information purposes.

Introduction

In 2003, the HIV Monitoring Foundation (HMF) has gradually reached its full personnel capacity. In the first quarter, the last organisational moves were made regarding its activation, such as finalising the last contracts with HIV treatment centres and consolidation of the financial and administrative organisation. Consequently, more attention could be paid to development as regards content. This resulted in the HMF's first scientific publications and presentations, including a detailed scientific report on HIV and AIDS in the Netherlands in December 2003, and execution of the HMF registration programme. The number of requests for using data from the HMF database grew; first results of research that was carried out using these data have become available in this year. National and international collaboration alike have proven to be highly productive; they have also become more structured over the past year.

A significant event in the relationship between the HIV Treatment Centres and the HMF was the introduction of a new database programme, which had become a necessity in order to be able to equally guarantee the quality of collected and yet-to-be collected data. By the end of 2003, implementation of this new programme, Oracle Clinical, was finished in the majority of HIV treatment centres, as well as the simultaneous education and training of data collecting staff. Moreover, several new, regularly employed data collectors were hired; the relatively large number of temp workers was substantially reduced. Finally, the year 2003 brought about a significant rise in the number of registered HIV patients: from 7,557 by the end of 2002 to 8.999 as per december 31, 2003. At the same time, significant changes in the HIV epidemic became apparent. In general, people infected with HIV tend to live longer than before. As a result, the number of patients treated with Highly Active Antiretroviral Therapy (HAART) increases. The number of antiviral agents in the HAART combination remains constant, as do the costs per patient. Another important change in the HIV epidemic in the Netherlands was the increasing number of patients that was infected through heterosexual contact. Remarkably, amongst the heterosexually infected patients, the population originating from Southern Africa is by now larger than the native Dutch population, Western-Europeans or North-Americans together. The figures provided by the HIV treatment centres confirm trends that are seen elsewhere ein Europe, too, including the growing number of relatively young women that contract the virus through heterosexual contact. The major deviation from these trends is the transmission of resistent HIV, which is still limited in the Netherlands.

We conclude that the number of new patients that are being included in the observational clinical HMF cohort is still on the rise. Thanks to the joint achievements of data collectors, data monitors and treating physicians in the dedicated HIV Treatment Centres we have at our disposal a substantial collection of data from HIV infected patients, whether treated with HAART or untreated, that can rightfully be called unique.

Amsterdam, March 29, 2004

Frank de Wolf, MD, PhD
Director HMF

Financial report

Financial report

Income

On 21 October 2002 the Minister of Health approved the HMF budget of a total amount of € 1,913,728, in full accordance with the expenditure established by the HMF Board of Governors. Based on this budget, a policy-rule for HIV monitoring – 'Beleidsregel HIV Monitoring' – was established by the Health Tariff Board (CTG), in which an extra provision was made for € 86,988 to be assigned to 22 HIV treatment centres established by the Minister of Health and, consequently, to be declared by the HMF.

Regarding variable costs, in our estimate for 2003 we had already taken into account 7,431 HIV infected patients in follow-up in each of the HIV Treatment Centres per July 1, 2002. The total number of patients in follow-up per December 31, 2003 turned out to have grown by 321 when compared to the number of patients in follow-up by mid-2002. Fixed costs in our estimate for 2003 were kept at the same level as in 2002.

In 2003, the administrative management of the DAD study (Data Collection on Adverse Events of Anti-HIV Drugs) was taken over from IATEC, for which compensation of € 102,414 was received. An appropriate project administration was set up especially for this purpose. Additional items were collected for the DAD study using case report forms that were adapted to specific DAD events. These events were monitored for the full 100% - as opposed to our regular 10% monitoring procedure.

Expenditures

Expenditures have generally followed the estimated budget. For the benefit of decentral data collection and subsequent data entry, € 89 per patient was transferred to the HIV Treatment Centres, with an exception for those HIV Treatment Centres which had outsourced these activities to the HMF (AMC-UvA, OLVG, UMCL and Ziekenhuis Walcheren). For the collection and subsequent storage of patient material, vital for the monitoring of resistance and changes in the HIV epidemic, a total of € 86,649 was transferred to the HIV Treatment Centres.

The largest expenditures by far are related to staffing. For the year 2003, a staffing estimate was made, including decentral data collection performed by SHM, of 18.6 full time equivalents (FTE), of which on average 17,89 FTE was filled, of which 2.0 FTE were not under contract with the HMF. 11.24 FTE were dedicated to the purpose of (decentral) data collection, data logistics and data management, while 3.0 FTE were dedicated to data processing and analysis. Finally, coordination and daily management of the HMF required 3.65 FTE in 2003. Other major material expenditures were for the licenses for the monitoring database, for the use of the AMC network and for the production of our scientific reports. Smoother sailing also reflects in numerical data as third-party related costs have been reduced by one quarter during 2003. Finally, the negative current account balance with the AMC has largely been repaid.

Reserve

Our financial reserve amounted to € 241,270 in the year 2003. It is our aim to increase this reserve further in order to be able to guarantee salary payments for a period of up to six months.

Balance sheet as of December 31, 2003 after allocation of results

	2003 (€)	2002 (€)		2003 (€)	2002 (€)
ASSETS			**LIABILITIES**		
Fixed assets			**Capital and reserves**		
Tangible fixed assets	0	0	General reserves	241,270	108,777
			Earmarked reserves for investments	-	110,285
			Earmarked reserves for DAD-study	92,340	-
	0	**0**		**333,610**	**219,062**
Current assets			**Short term liabilities**		
Debtors and accrued assets	7,167	764,533	Current account AMC	215,281	776,751
Cash	774,989	999,185	Current accounts HIV Treatment Centres Creditors	-	461,418
			Creditors	114,550	146,030
			Other short term liabilities and accrued expenses	118,715	160,457
	782,156	**1,763,718**		**448,546**	**1,544,656**
Total assets	**782,156**	**1,763,718**	**Total liabilities**	**782,156**	**1,763,718**

Profit and Loss Account 2003

	Result 2003 (€)	Budget 2003 (€)	Result 2002 (€)
Subsidy	1,913,737	1,913,729	1,760,556
Subsidy DAD study	102,412	0	0
Subsidy event registration DAD study	7,905	0	0
Total net revenue	**2,024,054**	**1,913,729**	**1,760,556**
Expenses storage patient materials	86,649	86,002	74,817
Expenses data collection	401,998	401,249	386,601
Expenses event registration DAD study	7,905	0	0
Personnel expenses	1,066,323	1,026,653	816,585
Depreciation on tangible fixed assets	129,570	0	15,428
Other operating charges	292,032	399,825	248,346
Total operating costs	**1,984,477**	**1,913,729**	**1,541,777**
Operating result	**39,577**	**0**	**218,779**
Financial income and expenses	22,552	0	283
Miscellaneous income and expenses	52,419	0	0
Total income and expenses	**74,971**	**0**	**283**
Result	**114,548**	**0**	**219,062**

Organisational report

Organisational report

HIV Treatment Centres

As per January 1, 2003, Medisch Centrum Alkmaar was officially appointed as an HIV Treatment Centre. This increased the total number of HIV Treatment Centres to 22. Four academic HIV Treatment Centres are acknowledged for treatment of paediatric HIV and AIDS. In total, 24 hospitals that are acknowledged by the Minister of Health are involved in the HIV Treatment Centres:

Academisch Medisch Centrum bij de Universiteit van Amsterdam
Academisch Ziekenhuis Groningen
Leids Universitair Medisch Centrum, Leiden
Academisch Ziekenhuis Maastricht
Universitair Medisch Centrum St. Radboud, Nijmegen
Universitair Medisch Centrum Utrecht
VU Medisch Centrum, Amsterdam
Erasmus Medisch Centrum, Rotterdam
St. Elisabeth Ziekenhuis, Tilburg
Kennemer Gasthuis Haarlem, location EG
Medisch Centrum Alkmaar
Medisch Spectrum Twente, Enschede
Onze Lieve Vrouwe Gasthuis, location Oosterpark, Amsterdam
Onze Lieve Vrouwe Gasthuis, location Prinsengracht, Amsterdam
Onze Lieve Vrouwe Gasthuis, location Jan van Goyen, Amsterdam
Slotervaart Ziekenhuis, Amsterdam
Medisch Centrum Haaglanden, location Westeinde, Den Haag
Leyenburg Ziekenhuis, Den Haag
Ziekenhuis Rijnstate, Arnhem
Medisch Centrum Leeuwarden
Ziekenhuis Walcheren, Vlissingen
Catharina Ziekenhuis, Eindhoven
Isala klinieken, locatie Sophia, Zwolle
Sint Lucas Andreas Ziekenhuis, Amsterdam

Wilhelmina Kinderziekenhuis UMCU, Utrecht
Emma Kinderziekenhuis AMC, Amsterdam
Sophia Kinderziekenhuis, EMC, Rotterdam
Academisch Ziekenhuis Groningen

Contractual arrangements are in place between HMF and each of these HIV Treatment Centres regarding the collection of demographical and epidemiological, as well as clinical, virological, immunological and pharmacological data of HIV infected patients that are being followed in any of these hospitals.

Internal organisation

During 2003, the HMF office was reorganised in order to better adapt its organisational structure to the tasks that it has to perform. Currently, it consists of a unit patient data and quality control (PD&QC) and a data processing and analysis unit (DPA). Data collectors employed by the HMF were assigned to the PD&QC unit; all activities regarding data collection are being coordinated here. Data monitors and the data inclusion/exclusion database are also assigned to this unit. Further, data management that is being performed by the Data Management Support (DMS) unit of the department Clinical Epidemiology and Biostatistics (CEB) of the AMC is also coordinated from this unit. In the second half of 2003, the task of managing this unit was assigned to a newly appointed manager PD&QC. As per December 31, 2003, the PD&QC unit consisted of 4,49 full time equivalents (FTE) for data monitoring, administration, QC and coordination; 6,38 FTE for decentral data collection performed by the HMF, and 0,5 FTE for temporary support of decentral data collection. In the course of 2003, the number of workers on a temporary contract was reduced drastically and replaced by a limited number of (part time) staff on a regular contract. Apart from a cost saving, this also helped to maintain the experience and know how that is available within the organisation, which is of importance for the quality of data collection and -entry.

The DPA unit currently consists of 3,0 FTE researchers in the fields of epidemiology, statistics and mathematical and analytical models. From October 2003, an additional 0,6 FTE was assigned to the DPA unit for the duration of six months for the purpose of performing a cost analysis of the treatment of HIV infected patients.

Finally, the HMF office is also home to the secretariat, financial and human resources administration and controlling, to the in- and external communication, as well as to the managing director. As per December 31, 2003, these activities altogether took up 3,65 FTE.

Data collection and QC report

Data collection

The following data are collected:

Identification of anonymised patient data (unique code)
Identification and coding of HIV Treatment Centre and the treating physician
Data on HIV transmission risks
Clinical data on HIV infection
Laboratory data on HIV infection
Data on antiretroviral therapy
Genotypic resistance data of HIV-1
Clinical data on side effects and toxicity of antiretroviral therapy
Data on co-medication

A protocol was developed for data collection regarding resistance, in which nucleotide and amino acid sequences of RT and the HIV protease gene is provided to the HMF and subsequently stored in a separate database. The majority of sequences were generated by the virological laboratories of AMC, UMCU, EMR and LUMC, where most HIV resistance determinations are performed in the Netherlands, and also by the virological laboratories of UMCN-St. Radboud, the VUMC and the Centraal Laboratorium voor Bloedtransfusie in Amsterdam. Quality checks regarding resistance assessment, as well as regular updating of interpretation schemes for newly found (combinations of) mutations and new antiretroviral agents, were taken care of by the HMF virology working group.

Privacy

Patient data were gathered in the course of their regular follow-up and/or treatment. Patients were informed about the possibility to object to, and thereby prevent, inclusion of their data in the HMF database. Patient data were stored under a unique code; other than gender and date of birth, no personal data was stored in the HMF database.

HMF database & data management

By the end of 2002, we began implementation of a new HMF database based on Oracle Clinical, which was specifically designed for clinical trials. Important arguments for implementing the new database were:

- Being able to maintain and improve the quality of included patient data over a long period of follow-up;
- Improving the safety of the database and the anonymous patient data stored in it;
- Improving the efficiency of data processing
- Improving patient privacy

Development of new data entry screens, adapted to the specific follow-up situation of the observational cohort while simultaneously optimising the database, lasted until May 2003. On May 12, we began installing Oracle Clinical and the parallel instruction of data collectors in the HIV Treatment Centres. During the planning process of installation and instruction, the availability of data collectors, IT staff and the quality and quantity of the data collection in the Treatment Centres were taken into account as much as possible. During 2003, Oracle Clinical was implemented on 20 out of 24 hospital locations. Implementation was postponed in the remaining four locations (Catharina Ziekenhuis, Eindhoven, Universitair Medisch Centrum Utrecht, Medisch Spectrum Twente, Enschede, Ziekenhuis

Rijnstate, Arnhem) as a result of technical problems on these locations. Data collectors in 18 hospitals were instructed; in total, 30 data collectors and 4 students were trained and coached by HMF data monitors to work with the new database.

The gradual implementation of the new database of course meant that from May, 2003, next to the new database the old Microsoft Access HIVREG database was still operational and in need of maintenance. This had certain consequences for data continuity, as a result of which new administrative procedures were designed. In collaboration with CEB, a central Microsoft Access database was set up in which HIVREG data of all hospitals was included. This database is used to centrally correct possible errors in the older data, but also and in particular for the production of periodical data merges and daily updating of local Access files that have existed since the ATHENA project in different HIV Treatment Centres. These local files often form the base for the presentation of overviews during clinical meetings in the Treatment Centres.

Quality control (QC)

On January 1, 2003, a random sample for 2003 was performed of 10% of already included patients, along with 10% of newly registered patients. As per January 1, 2003, 5,910 patients were included. During 2003, 593 of these were monitored, including 104 patients that were also monitored within the framework of the DAD study in connection with a cardiovascular accident (41) or death (63). In total, 100 newly registered patients were monitored for the first time in 2003.

Source data verification was performed prospectively on a total of 321 patients and retrospectively on 168 patients. On average, the Treatment Centres were visited 6,7 times by their assigned data monitor. During prospective monitoring of already registered patients it turned out that data quality had often decreased and that retrospective monitoring sometimes became a necessity. This was partly related to the number of patients that were followed up in a Treatment Centre and was often location-specific. Moreover, the quality of data collection and -monitoring appeared to be closely related to the specific know how of a particular data collector; it appeared that this specific knowledge was better developed among HIV/AIDS consultants and dedicated HMF data collectors than among employees who do not perform data collection on a full time basis and often have other, quantitatively more significant tasks to perform.

The fact that HIV Treatment Centres were on average visited twice as often as in 2002 was due in particular to the large number of data collectors that were in need of training and coaching. As an investment in future data quality, these trainings were performed on location as much as possible.

Consequently, each HIV Treatment Centre was assigned its own data monitor. Moreover, an investment was made in communication between data collectors and data monitors in order to improve the consistency of data collection even further. Through the use of electronic communication, contact between data collectors, data monitors and the QC manager has been intensified. The use of data from the new Oracle Clinical database enabled assessment of the specific training and coaching needs of particular data monitors. Thus, data monitors were enabled to resolve data-specific inconsistencies on-line.

It gradually became clear in the course of 2003 that current patient registration procedures involved too much administrative activity and that they were not entirely adequate for the relatively long follow-up duration of patients. Moreover, they did not contain adequate procedures for patients who change their treating physician or for those who are temporarily being followed up in a different Treatment Centre.

This situation has led to misunderstandings and problems with data processing and -analysis. Improvement of communication between the PD&QC and DPA units has lead to discussion of unresolved discrepancies by the data monitors and their respective Treatment Centres, and the effective resolution of these problems in the second half of 2003 by means of source-data verification.

Report Monitoring

Registration of HIV infected adult patients

The total number of cumulatively registered patients in the HMF database amounts to 8,999 patients. Of these patients, 8,317 (92,5%) are registered as being alive and 682 (7,6%) have died. As per December 31, 2003, data were monitored of 7,752 (86,2%) patients; for 679 (7,6%)

	Included as per 31-12-2003		Alive as per 31-12-2003		Dead as per 31-12-2003		Follow-up (incl. dead) as per 31-12-2003		No follow-up after 31-12-2002		Dead before 01-01-2003	
HIV Treatment Centre	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
AMC Amsterdam	1488	16.6	1366	91.8	122	8.2	1327	89.2	52	3.5	109	7.4
AZG Groningen	385	4.3	364	94.5	21	5.5	349	90.7	23	6	13	3.4
LUMC Leiden	287	3.2	271	94.4	16	5.6	265	92.4	9	3.2	13	4.6
AZM Maastricht	335	3.8	301	89.9	34	10.1	238	71.1	64	19.2	33	9.9
UMC St. Radboud Nijmegen	265	3	235	88.7	30	11.3	220	83.1	17	6.5	28	10.6
UMCU Utrecht	581	6.5	539	92.8	42	7.2	516	88.9	30	5.2	35	6.1
VUMC Amsterdam	236	2.7	204	86.4	32	13.6	178	75.5	30	12.8	28	11.9
EMC Rotterdam	1019	11.4	960	94.2	59	5.8	852	83.7	120	11.8	47	4.7
St. Elisabeth Ziekenhuis Tilburg	410	4.6	397	96.8	13	3.2	371	90.5	30	7.4	9	2.2
Kennemer Gasthuis/EG Haarlem	167	1.9	147	88.0	20	12.0	125	74.9	23	13.8	19	11.4
MCA Alkmaar	79	0.9	74	93.7	5	6.3	70	88.7	6	7.6	3	3.8
MST Enschede	192	2.2	170	88.5	22	11.5	166	86.5	7	3.7	19	9.9
OLVG Oosterpark Amsterdam	926	10.3	848	91.6	78	8.4	798	86.2	65	7.1	63	6.9
Slotervaart Amsterdam	611	6.8	554	90.7	57	9.3	509	83.4	58	9.5	44	7.3
MCH locatie Westeinde Den Haag	301	3.4	282	93.7	19	6.3	265	88.1	23	7.7	13	4.4
Leyenburg Den Haag	337	3.8	317	94.1	20	5.9	281	83.4	38	11.3	18	5.4
Ziekenhuis Rijnstate Arnhem	245	2.8	221	90.2	24	9.8	213	87	11	4.5	21	8.6
OLVG Prinsengracht Amsterdam	396	4.5	360	90.9	36	9.1	334	84.4	29	7.4	33	8.4
MCL Leeuwarden	101	1.2	97	96.0	4	4.0	92	91.1	6	6	3	3
Ziekenhuis Walcheren Vlissingen	62	0.7	57	91.9	5	8.1	51	82.3	6	9.7	5	8.1
OLVG locatie JvG Amsterdam	265	3	252	95.1	13	4.9	245	92.5	12	4.6	8	3.1
Catharina Eindhoven	145	1.7	143	98.6	2	1.4	131	90.4	14	9.7	0	0
Isala Klinieken/Sophia Zwolle	100	1.2	97	97.0	3	3.0	95	95	3	3	2	2
St. Lucas Andreas Amsterdam	66	0.8	61	92.4	5	7.6	61	92.5	3	4.6	2	3.1
Total	**8999**	**100**	**8317**	**92.5**	**682**	**7.6**	**7752**	**86.2**	**679**	**7.6**	**568**	**6.4**

Table 1: Registered adult patients per December 31, 2003 whose data the HMF is monitoring

HIV Treatment Centre	Included in 2003		Included in 2003; dead		Included in 2003; AIDS		Included in 2003; follow-up		Included in 2003; no follow-up		Included in 2003; no follow-up and dead	
	N	%	N	%	N	%	N	%	N	%	N	%
AMC Amsterdam	244	16.6	5	2.0	57	23.4	243	99.6	1	0.5	0	0
AZG Groningen	71	4.9	4	5.6	16	22.5	68	95.8	2	2.9	1	1.5
LUMC Leiden	38	2.6	1	2.6	13	34.2	37	97.4	1	2.7	0	0
AZM Maastricht	27	1.9	0	0.0	2	7.4	22	81.5	5	18.6	0	0
UMC St. Radboud Nijmegen	41	2.8	3	7.3	18	43.9	38	92.7	2	4.9	1	2.5
UMCU Utrecht	75	5.1	1	1.3	14	18.7	71	94.7	4	5.4	0	0
VUMC Amsterdam	35	2.4	0	0.0	7	20.0	28	80	7	20	0	0
EMC Rotterdam	191	13	3	1.6	26	13.6	124	65	67	35.1	0	0
St. Elisabeth Ziekenhuis Tilburg	35	2.4	0	0.0	3	8.6	34	97.2	1	2.9	0	0
Kennemer Gasthuis/EG Haarlem	22	1.5	1	4.5	4	18.2	22	100	0	0	0	0
MCA Alkmaar	16	1.1	0	0.0	2	12.5	16	100	0	0	0	0
MST Enschede	48	3.3	1	2.1	9	18.8	44	91.7	4	8.4	0	0
OLVG Oosterpark Amsterdam	255	17.3	9	3.5	64	25.1	220	86.3	32	12.6	3	1.2
Slotervaart Amsterdam	62	4.2	0	0.0	9	14.5	59	95.2	3	4.9	0	0
MCH locatie Westeinde Den Haag	43	3	0	0.0	3	7.0	41	95.4	2	4.7	0	0
Leyenburg Den Haag	46	3.2	1	2.2	11	23.9	37	80.5	9	19.6	0	0
Ziekenhuis Rijnstate Arnhem	33	2.3	2	6.1	4	12.1	33	100	0	0	0	0
OLVG Prinsengracht Amsterdam	43	3	0	0.0	2	4.7	39	90.7	4	9.4	0	0
MCL Leeuwarden	22	1.5	1	4.5	1	4.5	22	100	0	0	0	0
Ziekenhuis Walcheren Vlissingen	6	0.5	0	0.0	1	16.7	5	83.4	1	16.7	0	0
OLVG locatie JvG Amsterdam	22	1.5	0	0.0	4	18.2	21	95.5	1	4.6	0	0
Catharina Eindhoven	43	3	2	4.7	4	9.3	38	88.4	5	11.7	0	0
Isala Klinieken/Sophia Zwolle	39	2.7	0	0.0	4	10.3	39	100	0	0	0	0
St. Lucas Andreas Amsterdam	21	1.5	2	9.5	6	28.6	20	95.3	1	4.8	0	0
Total	**1478**	**101**	**36**	**2.5**	**284**	**19.3**	**1321**	**89.4**	**152**	**10.3**	**5**	**0.4**

Table 2: Patients that were included in 2003 and whose data the HMF is monitoring

this was not the case (Table 1). Discrepancies between hospital locations are substantial and are influenced by differences in timeliness of patient data entry. During 2003, the AZM, the EMC Rotterdam, the VUMC and the Leyenburgh hospital had a significant backlog in data entry. We estimate that between 3% and 5% may actually be lost to follow-up. Of course, no data were collected in 2003 of the 568 (6,4%) patients that had died prior to January 1, 2003.

The inclusion per hospital location during the year 2003 amounted to a total of 1,478 adults (Table 2). Of this group, 36 (2,5%) patients have died and 284 (19,3%) were diagnosed with AIDS. Of 152 (10,3%) patients, no follow-up data were (yet) monitored. This figure again shows large differences between different HIV Treatment Centres; the data entry backlog at Erasmus Medisch Centrum is once again confirmed.

Objection against inclusion	as per 31-12-2003		in 2003	
HIV Treatment Centre	N	%	N	%
AMC Amsterdam	8	4.8	4	3.9
AZG Groningen	5	3	1	1
LUMC Leiden	7	4.2	2	2
AZM Maastricht	3	1.8	1	1
UMC St. Radboud Nijmegen	4	2.4	2	2
UMCU Utrecht	25	14.9	8	7.7
VUMC Amsterdam	1	0.6	1	1
EMC Rotterdam	9	5.4	3	2.9
St. Elisabeth Ziekenhuis Tilburg	0	0	1	1
Kennemer Gasthuis/EG Haarlem	1	0.6	0	0
MCA Alkmaar	0	0	0	0
MST Enschede	2	1.2	3	2.9
OLVG Oosterpark Amsterdam	62	37	62	59.1
Slotervaart Amsterdam	6	3.6	1	1
MCH Westeinde Den Haag	12	7.2	5	4.8
Leyenburg Den Haag	19	11.4	7	6.7
Ziekenhuis Rijnstate Arnhem	2	1.2	0	0
OLVG Prinsengracht Amsterdam	0	0	1	1
MCL Leeuwarden	0	0	0	0
Ziekenhuis Walcheren Vlissingen	0	0	0	0
OLVG JvG Amsterdam	0	0	0	0
Catharina Ziekenhuis Eindhoven	0	0	1	1
Isala Klinieken Sophia Zwolle	1	0.6	2	2
St. Lucas Andreas Amsterdam	1	0.6	0	0
Total	**168**		**105**	

Table 3: Number of patients that have objected to the inclusion of their data in the HMF database

A total of 168 patients have withheld their consent for registration and inclusion of their data in the HMF database. An overview for each HIV Treatment Centre is presented in Table 3. The use of an informed consent procedure rather than an opt-out procedure largely explains the difference between these hospitals.

Registration of children exposed to or infected with HIV

In total, 77 children with an HIV infection have been registered. One of these patients has died. The median age in 2003 was 8 years (IQR 5-10 years). In 2003, 58 out of 76 children were younger than 12 years old; out of these, 32 are boys and 26 are girls. All of these are still alive. Almost 65% of these children are of Dutch origin; 27% originates from sub-Saharan Africa. Table 4 presents an overview of included children per HIV Treatment Centre.

Registration and monitoring of children's data has yet to reach sufficient levels. Consultation of the paediatrics involved on the implementation of data entry screens for the registration of children exposed to or infected with HIV has consumed significantly more time than we could foresee. These screens are currently being built; meanwhile, a number of HIV Treatment Centres has commenced registration of children.

Hospital	N	% of total
Emma Kinderziekenhuis AMC Amsterdam	27	35.07
AZG Groningen	1	1.3
LUMC Leiden	4	5.2
AZM Maastricht	2	2.6
Wilhelmina Kinderziekenhuis UMCU Utrecht	35	45.46
Sophia Kinderziekenhuis EMC Rotterdam	3	3.9
St. Elisabeth Tilburg	2	2.6
Slotervaart Ziekenhuis Amsterdam	1	1.3
Catharina Ziekenhuis Eindhoven	2	2.6
Total	**77**	

Table 4: Number of registered children exposed to or infected with HIV

Hospital	N	% as per 2003	N	% in 2003
AMC Amsterdam	128	29.23	23	29.88
AZG Groningen	31	7.08	4	5.2
LUMC Leiden	20	4.57	5	6.5
AZM Maastricht	6	1.37	0	0
UMC St. Radboud Nijmegen	18	4.11	4	5.2
UMCU Utrecht	40	9.14	7	9.1
VUMC Amsterdam	1	0.23	0	0
EMC Rotterdam	73	16.67	6	7.8
St. Elisabeth Ziekenhuis Tilburg	19	4.34	2	2.6
Kennemer Gasthuis Haarlem	9	2.06	5	6.5
MCA Alkmaar	5	1.15	1	1.3
MST Enschede	4	0.92	3	3.9
OLVG Oosterpark Amsterdam	18	4.11	1	1.3
Slotervaart Amsterdam	3	0.69	1	1.3
MCH Westeinde Den Haag	7	1.6	2	2.6
Leyenburg Den Haag	23	5.26	4	5.2
Rijnstate Arnhem	10	2.29	2	2.6
OLVG Prinsengracht Amsterdam	2	0.46	0	0
MCL Leeuwarden	3	0.69	1	1.3
Ziekenhuis Walcheren Vlissingen	1	0.23	0	0
OLVG JvG Amsterdam	2	0.46	1	1.3
Catharina Eindhoven	11	2.52	4	5.2
Isala Klinieken Sophia Zwolle	4	0.92	1	1.3
St. Lucas Andreas Amsterdam	0	0	0	0
Total	**438**	**100.1**	**77**	**100.08**

Table 5: Total number and number registered in 2003 of pregnant women infected with HIV

Registration of HIV infected pregnant women

A pregnancy was registered in a total of 438 HIV infected women (Table 5). In 75,3% of women, it was their first pregnancy. 19,2% of the cases were women who had been pregnant twice before, the remaining 4,5% had been pregnant more than twice before.

In 2003, 77 HIV infected pregnant women were registered, out of which 49 (63,6%) were diagnosed before pregnancy, and 28 (36,4%) were diagnosed during their pregnancy. 75,3% of all HIV infected women were of non-Dutch origin; 58,4% originated from sub-Saharan Africa. More than half (53,3%) of pregnant women with HIV were already being treated with HAART before pregnancy; 36,4% did not start treatment until their pregnancy. Duration of pregnancy in this group (2003) is shorter than 26 weeks in 11,7% of these women; in another 11,7% it is longer than 26 weeks. In 75,3% of the cases, the end of their pregnancy has not (yet) been registered.

In addition to the registration of children, data entry screens are currently being adjusted in order to improve registration and monitoring of pregnant women.

Monitoring of HIV infected adults

97,5% of HIV infected patients are infected with HIV Type 1. In 0,3% of patients a Type 2 infection has been registered; in the remaining 2,2% it is not known if they are infected with Type 1, Type 2 or Type 1 and 2. [1]. Of all patients included per December 31, 2003, 78% are male and 22% are female.

Median follow-up is 5,4 years (IQR 2,3-9,2); 5,6 (2,6-9,6) for men and 4,0 (1,7-7,9) for women. Median age for the entire cohort is 34 years (28-41). HIV infected women are median 6 years younger than men at the moment of HIV diagnosis. The number of new HIV diagnoses per year increased from 246 in 1990 to 878 in 2002. The percentage of women in the HIV infected population also steadily increased to 30,5% in 2003.

The composition of the HIV infected population registered by the HMF in the Netherlands is subject to change. A majority of patients is male and was infected through homosexual contact. However, the relative contribution of this group to newly diagnosed infections is declining; this development becomes most apparent in the group of men with homosexual contacts who are under 30. On the other hand, the number of new infections among homosexual men aged 30 or above increases slightly.

The picture looks quite different when it comes to heterosexual transmission. The relative contribution of native Dutch patients declines steadily. Virtually inversely proportional to this development is the steady rise of patients from sub-Saharan Africa. This trend is also seen in other Western European countries. In the group originating from sub-Saharan Africa, the proportion of women with an HIV infection is higher than that of men.

The frequency of visits to the treating physician has steadily declined from an average of 4,8 (SD 2,2) visits per year in 1999 to 3 (1,9) in 2003 (Table 6). The figure for 2003 may be subject to change because of the currently

	Frequency of visits (±SD)									
HIV Treatment Centre	**1999**		**2000**		**2001**		**2002**		**2003**	
AMC Amsterdam	5.3	(2.4)	4.7	(2.2)	4.6	(2.6)	4.1	(2.3)	3.7	(2.1)
AZG Groningen	6.4	(3)	4.9	(2.3)	5	(2.5)	4.9	(2.5)	4.1	(2.3)
LUMC Leiden	5.3	(2.3)	4.6	(2.4)	4.2	(2.5)	3.5	(2)	3.5	(1.8)
AZM Maastricht	4.4	(1.8)	4.6	(2)	4.7	(2.5)	4.1	(2.2)	2.6	(2)
UMC St. Radboud Nijmegen	6.1	(3.3)	5.1	(2.7)	5.5	(3.5)	5.3	(3.6)	4.3	(2.6)
UMCU Utrecht	4.3	(2.4)	4.3	(2)	4.1	(2.4)	3.6	(1.9)	2.8	(1.9)
VUMC Amsterdam	5.8	(2.5)	5	(2.6)	4.3	(2)	4	(1.7)	3	(2.6)
EMC Rotterdam	4.4	(1.4)	4	(1.5)	3.5	(1.6)	3	(1.5)	2.4	(1.4)
St. Elisabeth Ziekenhuis Tilburg	3.6	(1)	3.2	(1.1)	3.3	(1.2)	3.1	(1.4)	2.9	(1.3)
Kennemer Gasthuis/EG Haarlem	5.8	(3)	4.8	(2.3)	4.5	(2.6)	3.8	(2)	2.4	(2.2)
MCA Alkmaar	3.4	(1.3)	3.5	(1.3)	3.5	(2)	3.1	(1.4)	1.8	(1)
MST Enschede	6	(3.3)	5.1	(2.7)	5.5	(2.6)	5.4	(2.8)	5.2	(2.4)
OLVG locatie Oosterpark	4.3	(1.9)	4.1	(1.9)	3.6	(1.8)	3.2	(1.5)	2.4	(1.5)
Slotervaart Amsterdam	3.9	(1.6)	3.3	(1.5)	3	(1.6)	3.1	(1.6)	2.5	(1.5)
MCH Westeinde Den Haag	4.8	(2.2)	4	(2)	3.9	(2)	3	(1.4)	2.1	(1.4)
Leyenburg Ziekenhuis Den Haag	4.6	(1.4)	4.1	(1.8)	3.7	(1.6)	3.3	(1.5)	3.2	(1.8)
Ziekenhuis Rijnstate Arnhem	5	(1.8)	4.6	(1.7)	4.6	(1.9)	3.8	(1.8)	3.5	(1.7)
OLVG Prinsengracht Amsterdam	4.8	(2.2)	4.3	(2.3)	3.8	(1.7)	3.5	(1.9)	3	(1.7)
MCL Leeuwarden	3.9	(1.5)	3.8	(0.8)	4.3	(2.2)	3.8	(1.3)	3.1	(1.6)
Ziekenhuis Walcheren Vlissingen	4.8	(1.6)	4	(2.3)	4.2	(2.2)	4.7	(2.3)	2.5	(1.9)
OLVG locatie JvG Amsterdam	7	(1.4)	4	(1.8)	3.8	(1.4)	3.4	(1.8)	2.4	(1.2)
Catharina Ziekenhuis Eindhoven	3.7	(1.2)	3.9	(1.9)	3.3	(1.6)	4.2	(2)	4.3	(1.9)
Isala Klinieken/Sophia Zwolle	4.8	(1.5)	4.2	(2.2)	4.1	(2.4)	4.4	(1.4)	3.7	(2)
St. Lucas Andreas Amsterdam					3.8	(1.9)				
Total	**4.8**	**(2.2)**	**4.2**	**(2.1)**	**4**	**(2.2)**	**3.7**	**(2.1)**	**3**	**(1.9)**

Table 6: Annual frequency of visits to the treating physician

existing backlog of over 6 months in some HIV Treatment Centres. Nevertheless a clear increase can be observed in the total number of patients in follow-up, while the number of HIV/AIDS treating physicians remains relatively stable. As a result, the visiting frequency declines. In several HIV Treatment Centres, an AIDS nursing consultant in part handles patient visits. The HMF will in future also monitor these visits.

The number of measurements per year also declined. In 1999, CD4 cell counts in peripheral blood were on average measured 3,9 (1,8) times. In 2003, this had declined to 2,6 (1,7) times. For measurement of HIV RNA levels, these figures were 3,7 (2) and 2,6 (1,6), respectively. The consequences of these changes in the cost development of treatment of HIV infected individuals are discussed in the chapter 'Changing direct costs of HIV treatment since the introduction of HAART in on page 52 of this report.

The number of CD4 cells in the total registered population increases on average by 120 cells between 1996 and 2003 (Figure 1) whilst the percentage of patients with a plasma HIV RNA level to ≤500 copies/ml increases from 36,2% in 1996 to 71,4% in 2003 (Figure 2).

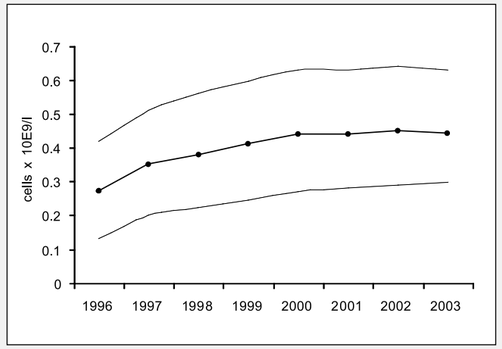


Figure 1: Average increase of CD4 + T cells in peripheral blood in the total HIV infected population after introduction of HAART in 1996

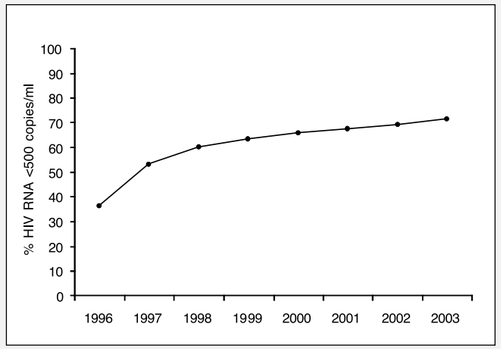
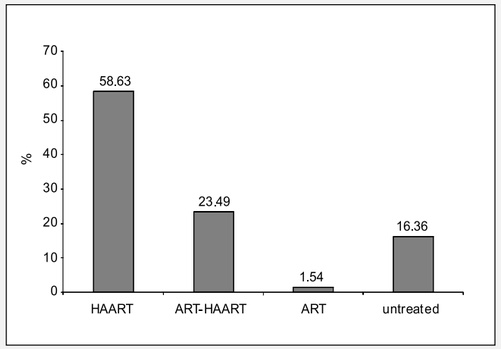


Figure 2: Increase in the percentage of patients with a decrease of HIV RNA to ≤500 copies/ml in plasma in the total HIV infected population after introduction of HAART in 1996

Initieel HAART regiem	2002 %	2003 %
AZT 3TC LOP/r	19.8	19.8
AZT 3TC NVP	14.1	15.3
AZT 3TC EFV	13.4	12.1
AZT 3TC ABC	10.7	7.9
AZT 3TC NFV	5.6	5.3
AZT 3TC ABC LOP/r	5.5	7.2
d4T 3TC LOP/r	3.7	1.2
AZT ddI IDV	3	2.8
TDF 3TC EFV	2.2	8.8
TDF 3TC NVP	2.2	3.7
AZT 3TC ABC EFV	1.8	2.8
d4T 3TC NVP	1.4	0.9
AZT 3TC KAL EFV	1.4	2.3
TDF ddI EFV	0.1	1.6
	84.9	91.7

Tabel 7: Meest gebruikt combinaties in de behandeling met HAART in 2002 en 2003

Out of the total population in follow-up during 2003, 82,1% was treated with HAART, 23,5% was pre-treated with a non-HAART combination of antiretroviral agents. Only 1,5% of patients were still treated with a non-HAART combination, while 16,4% were not treated at all (Figure 3). The most popular combinations of agents are included in Table 7. AZT + 3TC as a backbone in the HAART combination is used in 75% of treated patients. Lopinavir + ritonavir is added in 19% of the cases. Use of nevirapine and efavirenz remains stable between 12% and 14% during 2002 and 2003. The use of tenofovir becomes visible.



Figuur 3: Percentage of naive and pre-treated patiens on HAART, and non-HAART treated and untreated patiens as per 2003

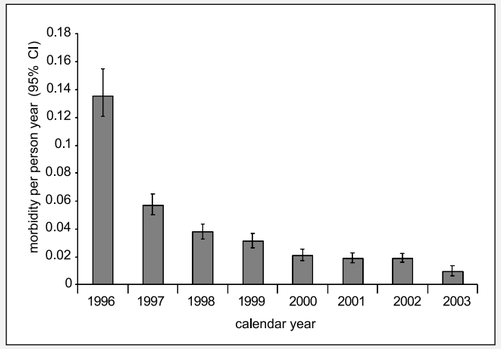


Figure 4: Morbidity per year

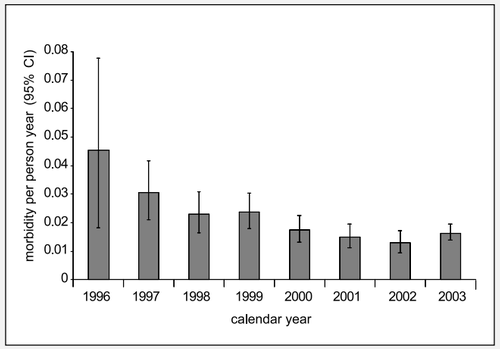


Figure 5: Mortality per calendar year

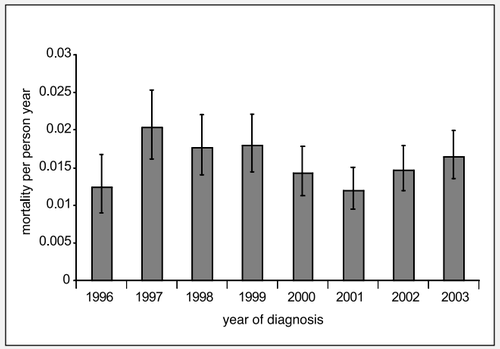


Figure 6: Mortality per year of diagnosis

Morbidity (Figure 4) among patients treated with HAART continues to decline from its introduction in 1996 onward and comes down to 0.01 per person year in 2003. Mortality in 2003 is 0,02 per person year and does not appear to decrease any further when compared to 2002 (Figure 5). Mortality per year of HIV diagnosis even increases slightly, from 0,01 in 2001 to 0,02 in 2002 and 2003, which may point to the fact that recently, patients are diagnosed at a later stage of their infection (Figure 6).

Report HMF registration programme
Following up on an earlier study into the changes in mortality and morbidity since introduction of HAART [2] a study was finished into the changes in mortality among HIV infected patients in collaboration with the Dutch Association of Insurers. Mortality ratios of treated HIV infected patients were compared with non-HIV infected Dutch population, matched for sex and age; prognostic survival models were developed for the initial effect of HAART. A high CD4 cell count after 24 weeks of HAART and commencement of HAART after 1998 turned out to be strongly associated with a higher 5-year survival chance. Moreover, mortality rates of HIV infected patients treated with HAART with a good immunological response were shown to be comparable with those of the non-infected Dutch population.

A study was performed among 1,156 therapy naive patients into temporary discontinuation of HAART, a phenomenon that is often observed in many patients. After median 9,1 (IQR 2,1-25,1) months of HAART, therapy was interrupted for 3,5 (IQR 1,1-13) months. Almost half of the patients had achieved plasma HIV RNA concentration of <500 copies/ml. At reinitiation of HAART, HIV RNA had increased in a vast majority of patients to values >500 copies/ml (median load 4,8log copies/ml). One year after reinitiation of HAART, 77% of the patients had once again reached an HIV RNA value of <500. We found that HAART treatment was less effective after reinitiation of therapy than before, and dependent on the immunological and virological condition that had been achieved prior to interruption.

The long-term effect of different regimes was studied in a sub-group of 849 therapy-naive patients that were treated with a HAART combination consisting of either a d4T+3TC or an AZT+3TC backbone in combination with either a NNRTI or one or two PIs, or the NRTI abacavir. The CD4 cell slope between 18 and 96 weeks of treatment was compared using mixed effect models. No difference was found between the two NRTI backbones. Preliminary results point at a higher slope than predicted in patients that achieved a CD4 count of 200/mm^3 after the first 18 weeks of treatment and that were treated with a combination of nelfinavir, saquinavir+ritonavir or indinavir+ritonavir in comparison to combinations with abacavir, neviparine and lopinavir+ritonavir. However, the lopinavir+ritonavir group turned out to be clinically worse at the outset of treatment than the other groups.

Research using the HIV RT and protease sequences that were available in mid-2003 showed that in 6% of the new infections in the Netherlands virus was transmitted with mutations that are known to cause resistance. Due to limitations of the research set-up - in particular, the inadequate availability of resistance data - it is possible that the transmission of resistance is currently being underestimated. In early 2004, resistance data of large numbers of patients were added to the HMF resistance database (Table 8).

	N sequences	
Virological laboratory	**ATHENA**	**HMF**
EMC Rotterdam	81	88
UMCU Utrecht	263	900*
LUMC Leiden	65	140
AMC Amsterdam	375	710
Total	**784**	**1838**

Table 8: Sequences gathered up to 2003 and included in the HMF database

* Estimated; sequences provided by the UMCU are still being processed

Toxicity in combination with the virological and immunological effect of frequently used HAART combinations was compared in a group of 3,524 therapy naive patients. Combinations with d4T+3TC as a backbone were stopped significantly more frequently as a result of toxicity than those with AZT+3TC; there turned out to be no difference in time to virological and immunological effect. Combinations with efavirenz and nepivarine were most effective virologically in comparison to abacavir, nelfinavir or lopinavir+ritonavir. On the other hand, the HAART combination with lopinavir+ritonavir was most successful immunologically. The AZT+3TC backbone, combined with abacavir, nelfinavir, lopinavir+ritonavir, neviparine or efavirenz, turned out to be less toxic than other combinations. This research is to be continued; in the future we will look at more recently introduced initial HAART regimes.

National collaboration

RIVM (Dr M Van der Laar)
Data are provided to RIVM regarding registration of new HIV infections in the framework of the national HIV registration and surveillance programme that is coordinated by RIVM [3].

The Amsterdam cohort studies (Prof Dr RA Coutinho, GG&GD, Prof Dr F Miedema, CLB-Sanquin; Prof Dr B Berkhout, Department of Human Retrovirology, AMC; Prof Dr JMA Lange, Department of Internal Medicine, AMC)
The HMF arranges the collection of clinical follow-up data, in particular data of participants of the cohort study among men with homosexual contacts.

Dutch Association of Insurers
The collaboration with the HIV/AIDS working group of the Dutch Association of Insurers focuses on a model-oriented approach of the question whether the chance of survival has increased since introduction of HAART and whether this is a ground for revision of the actuarial model currently in use in order to provide life insurance to HIV infected individuals. This collaboration started in 2002, was continued in 2003 and will - as far as this part is concerned - be finished in 2004.

International collaboration

DIDE: Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London (Prof Dr Roy Anderson). Between DIDE and the HMF, an agreement on scientific collaboration has been in place since 2002, which is aimed at statistical and mathematical support of DIDE to the HMF regarding analysis of observational cohort data on one hand, and execution of the HIV registration programme on the other.

An important goal of the DIDE research programme is to obtain more insight in the interplay of variables that determine the typical progress of infection in a host, as well as in the variables that determine the progress of infection in a particular population. In order to provide an answer to such research questions, techniques such as studying the qualities of non-linear differential equations, the organisation and management of large-scale field studies into transmission and control of an infection in populations, as well as analysis of large datasets are necessary.

Within this collaboration, first steps were taken towards researching changes in adherence during treatment of chronic HIV infection and their effects on the development of resistance. This research is performed in collaboration with the departments of Internal Medicine (Dr JM Prins and Prof JMA Lange) and Human Retrovirology (Dr S Jurriaans) of the AMC at the University of Amsterdam, the Department of Medical Psychology (Prof Dr GJ Kok) of the University of Maastricht and the Clinical Pharmacological Departments of the University Medical Centre Nijmegen, St. Radboud (Dr DM Burger) and Slotervaart Ziekenhuis Amsterdam (Prof Dr JH Beijnen).

ART: The Antiretroviral Therapy Cohort Collaboration (coordinated by Prof Matthias Egger, Department of Social and Preventive Medicine, University of Bern, Switzerland) is an international collaboration between (at this time) 13 cohort studies in Europe and North America. ART was initiated in order to assess the prognosis of therapy naive patients starting HAART. In Table 9, the cohorts are listed that are taking part in this collaboration as per October, 2002. For and on behalf of the HMF, Dr Frank de Wolf is the principal investigator for this collaboration.

Cohort	Country
French Hospital Database on HIV (FHDH)	France
Italian Cohort of Antiretroviral-Naive Patients (ICONA)	Italy
Swiss HIV Cohort Study (SHCS)	Switzerland
AIDS Therapy Evaluation project Netherlands (ATHENA)	The Netherlands
EuroSIDA	20 in Europe
Collaborations in HIV Outcomes Research US (CHORUS)	USA
Frankfurt HIV Cohort	Germany
Antiprotease Cohort (APROCO)	France
Aquitaine Cohort	France
British Columbia Centre for Excellence in HIV/AIDS	Canada
Royal Free Hospital Cohort	UK
South Alberta Clinic	Canada
Köln/Bonn Cohort	Germany

Table 9: Cohort studies that participate in the ART Cohort Collaboration

A follow-up study on the first results of this collaboration [4] was also published in the Lancet [5]. This study shows that the result achieved during the first 24 weeks of treatment is indicative for the outcome of treatment.

DAD: This collaboration between several different observational clinical cohorts is aimed at early recognition of cardiovascular problems that might be the result of HIV treatment with antiretroviral agents, in particular protease inhibitors. Dr DJ Lundgren (Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, Denmark) coordinates this study; Dr Peter Reiss (Department of Internal Medicine, AMC, Amsterdam) is the principal investigator on behalf of ATHENA/HMF for this study. In 2003, the HMF has taken over the executive responsibility for the collection of data for the DAD study. First results of the DAD study were published in 2003; they show a significant relation between the development of cardiovascular problems and the use of protease inhibitors [6].

PLATO (Pursuing Later Treatment Options): The number of patients that fail treatment on three different classes of antiretroviral agents is increasing. Their prognosis, and the factors that are associated with clinical progression, have not yet been adequately documented. In these patients, it is usually no longer possible to achieve adequate suppression of HIV replication below the detection limit. Consequently, the main purpose of treatment becomes the maintenance of CD4 levels in order to reduce the risk of disease progression. The PLATO (Pursuing Later Treatment Options) collaboration was developed within the ART Cohort Collaboration and therefore consists of the same 13 observational cohorts in Europe and in North America. Data on disease progression in patients after triple class virological failure are being collected. Dr Bruno Ledergerber (Division of Infectious Diseases, University Hospital Zurich, Switzerland) coordinates this study, Dr Peter Reiss (Department of Internal Medicine, AMC, Amsterdam) is the principal investigator on behalf of ATHENA/HMF for this study.

The purpose of this study is to be able to assess the predictive value of CD4 cell counts and viral load before mortality in these patients and to perform an analysis of predictors for changes in CD4 counts during follow-up. The results point at a significant mortality among patients who fail virologically after having been treated with agents from each of the three classes. Moreover, it appears that mortality is associated with low CD4 counts. Patients who remain on antiviral therapy while reaching a viral load, however measurable, below levels of 4log copies/ml plasma and who manage to achieve a 1-2log reduction compared to the start of HAART have a relatively good chance of preventing further immunological deterioration.

References

1. Gras L, Van Sighem AI, Van Valkengoed I, Zaheri S, De Wolf F, on behalf of the Netherlands collaborative HIV treatment centres. Monitoring of human immunodeficiency virus (HIV) infection in the Netherlands (2003). HIV Monitoring Foundation, Amsterdam, The Netherlands; 2003 Dec 1. Report No.: 2.

2. Van Sighem AI, Van De Wiel MA, Ghani AC, Jambroes M, Reiss P, Gyssens IC, et al. Mortality and progression to AIDS after starting highly active antiretroviral therapy. AIDS 2003 Oct 17;17(15):2227-36.

3. Op de Coul EL, Van Valkengoed I, Van Sighem AI, De Wolf F, Van der Laar MJW. HIV en AIDS in Nederland. Rijksinstituut voor Volksgezondheid en Milieu; 2003 Dec 1. Report No.: 441100018/2003.

4. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002 Jul 13;360(9327):119-29.

5. Egger M, Chene G, Sterne JA, May M, Costagliola D, Ledergerber B, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet 2003 Aug 30;362(9385):679-86.

6. Friis-Moller N, Sabin CA, Weber R, D'Arminio MA, El Sadr WM, Reiss P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 2003 Nov 20;349(21):1993-2003.

Costs of HAART

Changing direct costs of HIV treatment since the introduction of HAART in the Netherlands

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Abstract

Background

Tremendous savings in hospital-based AIDS care have been reported over the first few years since HAART became widely available in 1996. We determined whether this trend has stabilised or reversed over recent years.

Methods

The HIV Monitoring Foundation registers all HIV-infected patients in the Netherlands and collects data on antiretroviral drug use, co-medication and determination of HIV infection markers. In addition, we determined out-patient and in-patient hospital care consumption in the Academic Medical Centre (AMC) in Amsterdam. Standard costing procedures were used wherever possible, based on Dutch pharmacotherapeutic and health insurance guidelines. Costs (adjusted to 2002 euros) were expressed per person-year of follow-up after initiation of HAART for each half year up to July 2003.

Results

As of July 2003, 7,000 patients had initiated HAART, 1381 in the AMC. The national expenditure on HAART regimens has increased more than fivefold over the course of seven years, but expenditure per person-year of HAART has increased only modestly from € 8,800 in 1996 to € 9,600 in 2000 and has remained stable since. Costs of hospital resources decreased from over € 5,200 in 1996 to € 2,600 in 2000 and further declined to € 2,300 in the first half of 2003. Subgroup analyses indicated that the costs of in-patient hospital care and expenditure on co-medication have increased recently among patients who started HAART in 1997. The costs of treatment were markedly high during the first year of HAART among patients who initiated therapy in 2000.

Conclusions

On a population level, the per capita costs of HAART in the Netherlands have continued to decrease up to July 2003, but seemed to have reached a nadir. Long-term use of HAART is associated with increased expenditure on in-patient hospital resources and initiation of HAART appears more expensive nowadays than previously reported.

Introduction

Antiretroviral combination therapy, also known as highly active antiretroviral therapy (HAART), entered Dutch clinical practice in 1996 [1–3]. Combinations initially existed of nucleoside analogues for the inhibition of the HIV encoded enzyme reverse transcriptase (NRTIs) and inhibitors of the protease enzyme (PIs). Non-nucleosides for the inhibition of reverse transcriptase (nNRTIs) arrived in 1998 as a third drug class of choice in the antiretroviral treatment of HIV infection [4]. At the same time, it was proposed to increase the number of drugs combined in one regimen in order to attain maximum suppression of viral replication [5]. More recently, acknowledgments of the limitations and long-term complications of HAART have led to more restrictive guidelines for the initiation of antiretroviral therapy as well as the concept of structured treatment interruptions. Adverse effects of antiretroviral drugs pose a serious problem for long-term adherence to HAART, with potential consequences for the development and possibly transmission of drug-resistant HIV strains [6–9].

Ongoing introduction of new antiretroviral drugs and increasing insights into the adverse effects of HAART have affected the relative popularities of the many different available regimens. The population treated with HAART in the Netherlands is subject to change as well. Due to the increased survival of HIV infected people since the introduction of HAART, the prevalence of people with long-term HIV infection has increased. A marked change in demography has been noticed among people newly diagnosed with HIV, with a consistently increasing share of women and/or immigrants from outside of the European Union [10].

The first integral report on the HIV epidemic in the Netherlands since the introduction of HAART was published in September 2001 [11]. It was concluded that the use of combination antiretroviral regimens had led to significant cost savings in the care for HIV infected people. Moreover, the direct medical costs of HIV treatment per person-year of follow-up after initiating HAART had continued to decrease from 1996 up to 2000.

The HIV Monitoring Foundation (HMF) was established in 2002. HMF registers all HIV infected patients in the Netherlands and collects data on the use of antiretroviral drugs, co-medication and the measurement of HIV infection markers. In light of the changing composition of the Dutch population treated with HAART and the increased complications due to HAART, we investigated whether the direct medical costs of HAART have further decreased, stabilised or increased over recent years. To this end, a trend analysis was performed over the entire period from July 1996 until July 2003.

Methods

Cost components

We identified the following components for an economic evaluation of HAART: antiretroviral drug use; use of co-medication against opportunistic infections, malignancies or side-effects of antiretroviral drugs; clinic visits and consultations; and hospital-based care for the treatment of AIDS-related diseases or complications due to HAART.

The Dutch HIV Monitoring Foundation takes care of the national registry of all people diagnosed with HIV infection in the Netherlands. The registry combines data from 25 hospitals, including 8 academic hospitals, located in different parts of the country. For an economic evaluation of HAART, we only considered those patients who had initiated an antiretroviral regimen that was classified as HAART: any combination of drugs from at least 3 different classes or a triple NRTI regimen containing abacavir (ABC).

Data on the use of antiretroviral drugs and co-medication, as well as the determination of virology, immunology, serology and haematology from peripheral blood, were derived directly from the HMF Oracle Clinical database, described in detail elsewhere [10]. Data on hospital-based out-patient and in-patient care (including all diagnostic and therapeutic procedures involved) were derived from the registry of the Academic Medical Centre (AMC) in Amsterdam. This hospital takes care of the largest group of HIV-infected patients in the Netherlands. According to the HMF registry, a total of 7,000 persons in the Netherlands had started HAART before July 2003. Of these, 3,629 attained most recent clinic visits at an academic hospital and 1,381 (i.e., 1 in 5 of all HIV infected patients treated with HAART in the Netherlands) were treated in the AMC.

Unit prices

Antiretroviral drugs and co-medication were priced according to the Dutch Farmacotherapeutisch Kompas, edition 2002 [12]. For every drug we calculated a fixed price per day based on standard recommended dosage.

Unit prices for clinic visits, specialist consultations and in-patient days (both day care and hospitalisation, including psychiatric wards) were derived from the literature [13,14]. Although we only had data on registered care consumption in the AMC, we extrapolated those

volumes to other hospitals and weighted the costs according to the proportions of patients most recently treated in academic versus non-academic hospitals.

Unit prices of determining plasma viral load and genotypic drug resistance had been calculated previously, based on detailed cost data available in the AMC hospital ledger and buying department [11]. The unit price calculation included both fixed (e.g. hospital infrastructure and administration) and variable (e.g. materials and personnel) costs. Unit prices of other peripheral blood determinations (e.g. CD4/CD8 T lymphocyte counts, differential haematology, measurement of viruses other than HIV, clinical chemistry) were based on standard tariffs derived from national registries. Costs of hospital-based diagnostic and therapeutic procedures were based on tariffs recommended by the Dutch health insurance guidelines. For a substantial number (volume 30%) of diagnostic and therapeutic procedures, no standard recommended tariff was available. As the evaluation presented here takes an economic rather than a financial perspective, the 5% trimmed mean was taken as a proxy for the unit price of these procedures.

Data analysis

Resources used and corresponding costs were quantified in terms of national expenditure in case data were derived from the HMF Oracle Clinical database. For data derived from the registry of the AMC, resource use and costs were expressed per person-year of follow-up in the AMC, based on patient information available within the HMF registry. Only those patients who were treated with HAART in the AMC for their entire follow-up were included in person-year analysis. All results were aggregated per half year over the seven-year period from July 1996 until July 2003, with observation time starting at initiation of HAART. Unless a death notification was received, we considered patients to be in follow-up until 3 months after the last available information. This corresponds to the average time between scheduled clinic visits.

Costs were expressed per person-year of follow-up for each half-year interval, as follows. The total number of person-years for each of the 14 half year intervals was calculated from the duration of follow-up of all patients using HAART in the particular interval. The volumes of resource used within a half-year interval were multiplied by the respective resource unit prices and this was divided by the total number of follow-up. Using person-years of follow-up in the denominator automatically accounts for the natural inflow and outflow of patients in the Dutch HAART population.

We did not account for price fluctuations in the costs of the various care components. Although these price fluctuations may have been substantial in some cases, the prices of antiretroviral drugs have remained relatively robust since their introduction in the nineties. Nonetheless, we wanted to emphasise the trends in resource use over time rather than the financial trends, and for this reason we used fixed unit prices. All costs were adjusted to 2002 euros.

Data were analysed using the SAS statistical package, version 8.02 for Windows.

Results

Characteristics of the HAART population in the Netherlands

As of July 2003, a total of 7,000 patients had initiated HAART in the Netherlands. Among those, 5,520 (79%) were male of whom 3,773 (68%) were homosexual. Median age at start of HAART was 37 years, with an inter-quartile range from 31 to 44 years. In the second half of 1996, HAART was used by 1,688 HIV infected patients in the Netherlands. This number increased to 2,875 in the second half of 1997, and further increased to 3,585 in the second half of 1998. Since then, the Dutch HAART population has shown a constant increase, rising with approximately 600 each year. In the second half of 2002, 6001 patients were registered as treated with HAART. Due to incomplete data entry and verification at the time of analysis, the figure of 6216 likely underreports the total number of patients on HAART in the Netherlands for the first half year of 2003.

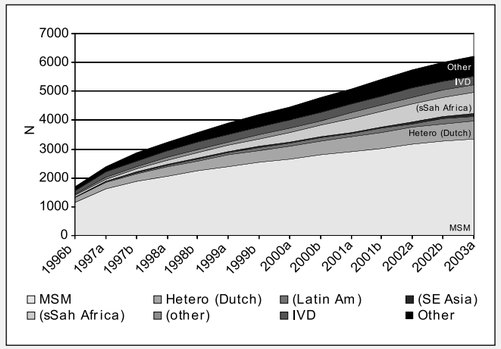

Figure 1: Prevalence of HAART use in the Netherlands from July 1996 until July 2003

Legend: MSM (men who have sex with men): infected via homosexual transmission; Hetero: infected via heterosexual transmission (region of origin in brackets); IVD: infected via intravenous drug use; Other: includes unknown routes of transmission. First and second half of each year is indicated by a and b, respectively. Prevalence estimates include all patients who initiated HAART before the end of the interval or had initiated HAART before and were still in follow-up by the beginning of the interval.

Remarkable is the ever increasing share of patients who have acquired HIV via heterosexual contact (Figure 1). In this group, the large number of patients from sub-Saharan African origin is especially striking. The share of HIV infected people treated with HAART from South-East Asia is small. The number of homosexual men using HAART has continued to increase since 1996. This is partly due to the improved survival of patients who already were infected with HIV before 1996, and partly due to a steady number of new HIV diagnoses (250–350 each year) among homosexual men since 1996. In contrast, the number of intravenous drug users (IVD) using HAART has remained stable over the years.

National expenditure on HAART regimens

A number of antiretroviral drugs that have been used did not become available in standard clinical practice. For these drugs, we could not obtain a unit price. Because their collective volume was only 0.12% of the total number of days that antiretroviral drugs were prescribed between July 1996 and July 2003, we ignored their contribution to the costs of HAART regimens.

The average number of drugs used in combination increased from 2.97 in the second half of 1996 to 3.23 in 2000. Since then, this number has shown a slight decrease to 3.17 in the first half of 2003. Since 1996, patients have interrupted antiretroviral therapy for increasing amounts of time. Treatment interruptions accounted for 4.3% of follow-up in the second half of 1996, whereas they accounted for 8.7% of follow-up in the second half of 2000. Since then, the proportion time off antiretroviral drugs has remained constant per person-year of follow-up. The costs of antiretroviral drugs per person-year of follow-up, including treatment interruptions, have increased from € 8,832 in the second half of 1996 to € 9,613 in the second half of 1998. In 1999, the costs of antiretroviral drugs temporarily declined below € 9,500, but have remained stable between € 9,500 and € 9,600 per person-year since 2000.

The total costs of HAART regimens have increased more than fivefold over the seven years since their introduction in 1996 (Figure 2). National expenditure rose from 5.4 million euros in the second half of 1996 to 28.3 in the first half of 2003. The increased expenditure since 2000 is mainly attributable to HAART regimens involving triple NRTIs, coinciding with the introduction of trizivir. This single pill combines the NRTIs zidovudine (AZT), lamivudine (3TC) and abacavir (ABC). In terms

of popularity, the nNRTIs nevirapine (NVP) and efavirenz (EFZ) have surpassed the popularity of PIs for the first time in 2003. Because of their slightly higher daily prices, PIs nonetheless still constitute a higher total cost as compared to nNRTIs.

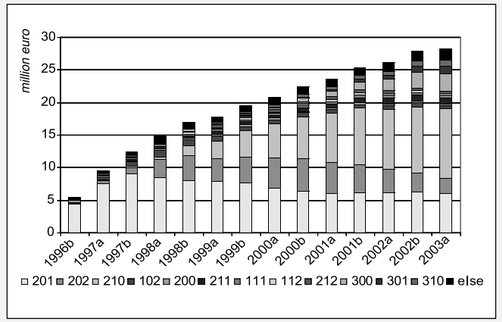

Figure 2: Total costs of HAART regimens in the Netherlands from July 1996 until July 2003

Legend: HAART regimens are coded as follows: the first figure denotes the number of NRTIs included, the second the number of nNRTIs and the third figure denotes the number of PIs included, e.g. 210: 2 NRTIs + 1 nNRTI; 102: 1 NRTI + 2 PIs. First and second half of each year is indicated by a and b, respectively. Numbers of patients for each half year are as in Figure 1.

Hospital care consumption after initiating HAART

The frequency of out-patient clinic visits decreased from 7.8 per person-year of follow-up in the second half of 1996 to 4.0 over the year 2000. The frequency of out-patient clinic visits has further decreased over recent years, but seems to have reached a nadir at one visit in 3 to 4 months. Coinciding with the decreasing frequency of out-patient clinic visits, the number of T lymphocyte counts and plasma viral load determinations decreased from between 5 and 6 per person-year of follow-up in the second half of 1996 to 3.3 in the first half year of 2003. By contrast, the frequency of peripheral blood testing for clinical chemistry or haematology has remained stable around 3.0 tests per person-year of follow-up since 1997. Genotypic drug resistance was determined at a frequency well below 0.1 per person-year of follow-up once HAART was initiated. Because the unit price of determining genotypic drug resistance is in the order of plasma viral load quantification, yet its frequency is so much lower, we ignored its contribution in cost analysis.

The frequency of consultations with specialists, other than the AIDS treating physician, decreased from 14.4 per person-year of follow-up in the second half of 1996 to 6.8 in the first half year of 2003. This decrease was entirely due to a decrease in the number of consecutive consultations, for the number of primary consultations remained stable at a frequency of 0.5 per person-year of follow-up once HAART was initiated. The frequency of inter-collegial consultations neither changed over time, remaining between 1 and 2 per person-year of follow-up from July 1996 to July 2003. From 1998 onwards, the hospital pharmacy has been consulted more frequently than all other specialists taken together. However, the frequency of consultations with the hospital pharmacy has decreased since 1998 as well, from 7.1 in the first half of 1998 to 4.5 in the first half year of 2003. Consultations with other specialist decreased from 3.8 to 2.3 per person-year of follow-up over the same period.

The number of hospital in-patient days within the AMC decreased from 6.7 days per person-year of follow-up in the second half of 1996 to 1.1 in the first half of 2003. Both the number of day care treatments and the number of hospitalisations have decreased over time. From 1998 onwards, the frequency of day care treatment was always below that of hospitalisation. Since 1999, the frequency of day care treatment remained below 0.1 per person-year of follow-up, whereas the frequency of hospitalisation stayed between 0.1 and 0.2 per person-year of follow-up. The length of hospital stays showed a small decrease over time as well. In 1997, hospitalisation was followed by 11.3 in-patient days on average. In 2002, the average duration of a hospital stay was 8.4 days.

Per capita costs of HIV treatment after initiating HAART

Hospital costs of HIV treatment once HAART had been initiated still amounted to € 5,095 per person-year of follow-up in the second half of 1996. In the second half of 1999, hospital costs of HIV treatment during HAART decreased to less than € 3,000 per person-year of follow-up and have since stayed at this level. Costs of hospital resource use have slightly declined in recent years, from € 2,622 in 2000 to € 2,567 in 2001 and further to € 2,298 in 2002. In the first half of 2003, hospital care of HIV treatment cost € 2,306 person-year of follow-up (Figure 3).

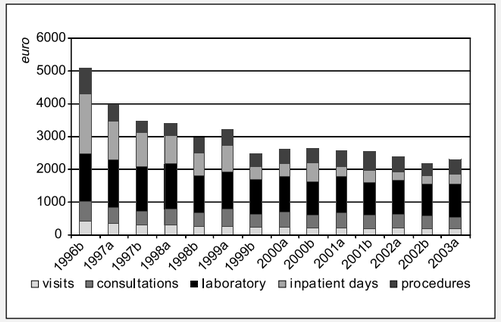

Figure 3: Costs of hospital resource use per person-year of follow-up after initiating HAART

Legend: Cost estimates for (out-patient clinic) visits are based on the subgroup of patients who were treated with HAART in the AMC (N=1381; 5490 person-years of follow-up after initiating HAART). Cost estimates for consultations, in-patient days and (diagnostic and therapeutic) procedures are based on those patients for whom data on in-patient hospital care consumption was available (N=599; 2894 person-years of follow-up after initiating HAART). Laboratory costs include most common serological, haematological, virological and immunological measurements, with estimates based on all patients in follow-up with HMF (see Figure 1 for numbers). First and second half of each year is indicated by a and b, respectively.

The costs of medication other than antiretroviral drugs decreased over time once HAART was initiated. In the second half of 1996, expenditure on co-medication was € 1,389 per person-year of follow-up. In the first half of 2000, co-medication during HAART cost only € 377 per person-year of follow-up. Co-medication costs have risen in recent years, but the increase is small when seen on a population level, amounting to € 421 per person-year of follow-up in the first half of 2003.

The initial decrease in the costs of co-medication was compensated for by increased expenditure on HAART regimens until 1999. Total drug costs have remained remarkably stable over the seven years since introduction of HAART. Average expenditure on drugs was € 10,014 per person-year of follow-up after initiating HAART. To illustrate the stability of total expenditure on drugs, the minimum was € 9,880 (in the second half of 2001) whereas the maximum was € 10,242 (in the first half of 1998). Thus, total medication costs have fluctuated within a very narrow range since the introduction of HAART.

As a consequence of stable medication costs, the share of hospital care components in the direct costs of HIV treatment has progressively decreased over time. In the second half of 1996, hospital resource use still accounted for 33% of total HIV treatment costs once HAART was initiated. In the first half of 2003, hospital resource use accounted for 19% of total HIV treatment costs per person-year of follow-up.

The declining per capita costs of HIV treatment are caused by an increasing number of patients in longer follow-up for whom HAART has proven successful. However, subgroup analysis indicated that expenditures on co-medication and the costs of in-patient care have increased recently in the cohort of AMC patients who initiated HAART in 1997 (Figure 4). Also, it seems that

the costs of hospital-based care in the first year of treatment are higher for cohorts that started more recently, as evidenced by the cohort of AMC patients who initiated HAART in 2000 as compared to 1997 (Figure 4). Annual costs of HIV treatment nonetheless declined rapidly, and in 2002 the cohort of patients who initiated HAART in 1997 consumed altogether more hospital resources than the cohort that started in 2000 (Figure 4). Data from other hospitals are needed to assess whether these patterns are general. Longer follow-up will prove whether the trends observed will hold for cohorts of patients who have initiated HAART more recently.

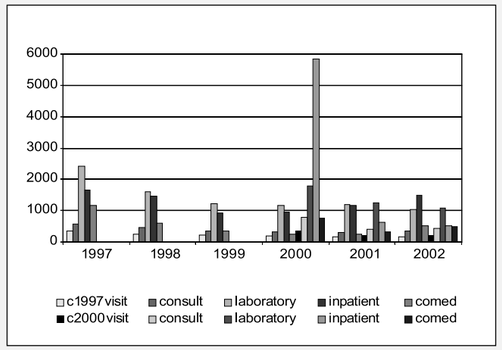

Figure 4: Costs (in euros) of hospital-based care for HIV infected patients treated in the Amsterdam Academic Medical Centre (AMC) per person-year after initiating HAART in 1997 or in 2000.

Legend: ©1997: cohort of patients who initiated HAART in 1997 in the AMC. Cost estimates for out-patient care (clinic visits, laboratory measurements and comed: co-medication) are based on the entire group of patients (N=223; 1331 person-years of follow-up after initiating HAART), while cost estimates for in-patient care (consult: consultations, in-patient: in-patient days plus procedures) are based on those patients for whom data on in-patient hospital care consumption was available (N=123; 757 person-years of follow-up after initiating HAART). Numbers for the 2000 cohort are N=125 (402 person-years of follow-up after initiating HAART) for out-patient care and N=29 (87 person-years of follow-up after initiating HAART) for in-patient care.

Discussion

The rising costs of HIV treatment in the Netherlands are attributable to the ever growing population of HIV infected persons treated with HAART. National expenditure on HAART regimens has increased more than fivefold over the seven years since HAART entered clinical practice in 1996. However, the per capita costs of antiretroviral drugs have not increased over recent years, and total drug expenditure has remained remarkably stable since 1996 at € 10,000 per patient per year once HAART was initiated. The per capita costs of hospital-based care have continued to decline since the introduction of HAART. On a per capita basis, the direct costs of HIV treatment seem to have reached their nadir at € 12,500 per patient per year after initiating HAART.

The presented figures constitute minimum estimates. We based our entire analysis on registered volumes of drug use and hospital care consumption, the latter derived from the information system of the AMC. Because a few components are missing from the analysis, notably radiological procedures and extramural care, it may be that the true costs of HIV treatment are somewhat higher than we estimated. It is unlikely that these components constitute a large portion of the direct costs of HIV treatment, although it is possible that extramural care for HIV infected patients has somewhat increased over recent years in keeping with the improved health status of most HIV infected patients. Non-academic hospitals may show a different pattern of care consumption, but this will not substantially alter the trends on the population level as most of the patients in the Netherlands are treated with HAART at an academic hospital.

Soon after protease inhibitors entered clinical practice it became clear that the costs of HIV treatment shifted from in-patient medical care to out-patient pharmaceutical care [15,16]. Also, it seemed that the costs of HIV treatment, when viewed per person-year of seropositive follow-up, increased only marginally after introduction of HAART [15–17]. Lifetime treatment costs for HIV infected patients became higher as a result of prolonged life-expectancy, but judged against the gain in quality of life the cost increase was deemed cost-effective in comparison to previously available dual nucleoside regimens [18]. We focused on the direct costs of HIV treatment once HAART was initiated, and found that these have continued to decrease over time on the population level in the Netherlands. The declining costs of HIV treatment once HAART is initiated could be due to an increased efficacy of HAART regimens over time, as we have shown in a previous report [10]. Experience with HAART on part of the medical personnel could have led to a more efficient use of resources as well, but the most obvious factor is the increasing proportion of HIV infected patients for whom HAART has proven successful. Examination of direct costs in a German cohort that initiated HAART in 1997 found a continuous decrease of expenditures for non-HAART drugs, diagnostics and hospitalisation. Consequently, HAART caused about one half of total direct costs in 1997 and two third in 2001, respectively [19].

The estimated costs of HIV treatment in the Netherlands are comparable to estimates from other Western countries. Direct medical costs of HIV treatment were $ 17,000 per patient in the year 1997/1998 in the USA [17,20]. Over the same year, we estimated a figure of € 13,500 in the Netherlands, or $ 16,000 according to the value of the euro upon its introduction in January 1999. In Italy, the direct costs of HIV treatment were estimated at $ 14,000 over the year 1997/1998 [21], and at € 12,000 in the year 1998 [22]. The difference to our estimate is likely due to the fact that we conditioned the analysis on patients treated with HAART regimens, with likewise higher expenditure on antiretroviral drugs. The direct costs of HIV treatment in Canada have been estimated between € 9,000 and € 10,000 per patient in 2000/2001 [23]. Again, this study did not restrict the analysis to patients treated with HAART regimens and antiretroviral drug expenditure only accounted for 69% of total costs. In comparison, we estimated the costs of HIV treatment in 2000/2001 at € 12,600 per patient, of which 76% was for antiretroviral drugs.

On the population level, the decline of direct costs of HIV treatment seems to have reached a nadir. Subgroup analyses indicate that long-term use of HAART may be associated with increased expenditures on co-medication and hospitalisation, which could be due to an increased incidence of HAART-related complications. Moreover, initiation of HAART appears more expensive in recent years than it was in the late nineties. This could be due the trend to defer HAART to progressively later stages of infection and to the fact that HIV is diagnosed in more advanced stages of infection among a growing proportion of people, notably male immigrants from outside of the European Union. Initiating HAART at low CD4 cell count and high plasma viral load is associated with increased risk of disease progression and mortality [24–26]. Ongoing registration and economic evaluation of HIV treatment are required to prove whether the same patterns hold for hospitals other than the AMC and to signal trend changes in time.

References

1. Borleffs JC, Esseveld F, Hoepelman IM, Boucher CA. AIDS; new developments. II. Treatment of HIV infection. Ned Tijdschr Geneeskd. 1997, 141:1036-43.

2. De Wolf F, de Jong JJ, Hertogs K, Danner SA, Lange JM, Goudsmit J. Virological evaluation of treating HIV infected patients with (combinations of) antiretroviral drugs at the Amsterdam Academic Medical Centre, 1996/'97. Ned Tijdschr Geneeskd. 1998, 142:573-8.

3. Wit FW, van Leeuwen R, Weverling GJ, Jurriaans S, Nauta K, Steingrover R, Schuijtemaker J, Eyssen X, Fortuin D, Weeda M, De Wolf F, Reiss P, Danner SA, Lange JM. Outcome and predictors of failure of highly active antiretroviral therapy: one-year follow-up of a cohort of human immunodeficiency virus type 1-infected persons. J Infect Dis. 1999, 179:790-8.

4. Nederlandse Vereniging van AIDS Behandelaren. Richtlijn antiretrovirale behandeling in Nederland. CBO 2000.

5. Weverling GJ, Lange JM, Jurriaans S, Prins JM, Lukashov VV, Notermans DW, Roos M, Schuitemaker H, Hoetelmans RM, Danner SA, Goudsmit J, De Wolf F. Alternative multidrug regimen provides improved suppression of HIV-1 replication over triple therapy. AIDS. 1998, 12:F117-22.

6. Jambroes M, Weverling GJ, Reiss P, Danner SA, Jurriaans S, Ten Veen JH, Van der Ende ME, Schutten M, Schneider MM, Schuurman R, Mulder JW, Kroes AC, Lange JM, De Wolf F; Kliniek en Virologie van het ATHENA-project. HIV-1 therapy in the Netherlands; virological and immunological response to antiretroviral therapy. Ned Tijdschr Geneeskd. 2001, 145:1591-7.

7. Nieuwkerk PT, Sprangers MA, Burger DM, Hoetelmans RM, Hugen PW, Danner SA, Van der Ende ME, Schneider MM, Schrey G, Meenhorst PL, Sprenger HG, Kauffmann RH, Jambroes M, Chesney MA, De Wolf F, Lange JM; ATHENA Project. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. Arch Intern Med. 2001, 161:1962-8.

8. De Ronde A, van Dooren M, Van der Hoek L, Bouwhuis D, de Rooij E, van Gemen B, De Boer R, Goudsmit J. Establishment of new transmissible and drug-sensitive human immunodeficiency virus type 1 wild types due to transmission of nucleoside analogue-resistant virus. J Virol. 2001, 75:595-602.

9. Goudsmit J, Weverling GJ, Van der Hoek L, de Ronde A, Miedema F, Coutinho RA, Lange JM, Boerlijst MC. Carrier rate of zidovudine-resistant HIV-1: the impact of failing therapy on transmission of resistant strains. AIDS 2001, 15:2293-301.

10. Gras L, Van Sighem AI, Zaheri S, Van Valkengoed IG, De Wolf F. Monitoring of Human Immunodeficiency Virus (HIV) infection in The Netherlands. Stichting HIV Monitoring 2003.

11. De Wolf F, Lange JM, Bossuyt PM, Dijkgraaf MG, Burger DA, Nieuwkerk PT, Reiss P (editors). Monitoring of human immunodeficiency virus type 1 (HIV-1) infection in The Netherlands. ATHENA 2001.

12. Commissie Farmacotherapeutische Hulp. Farmacotherapeutisch Kompas. College voor Zorgverzekeringen 2002.

13. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Standardisation of costs. The Dutch manual for costing in economic evaluations. Pharmacoeconomics 2002, 20:443-54.

14. Oostenbrink JB, Buijs-van der Woude T, Van Agthoven M, Koopmanschap MA, Rutten FFH. Unit costs of in-patient hospital days. Pharmacoeconomics 2003, 21:263-71.

15. Mouton Y, Alfandari S, Valette M, Cartier F, Dellamonica P, Humbert G, Lang JM, Massip P, Mechali D, Leclercq P, Modai J, Portier H. Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centres. Federation National des Centres de Lutte contre le SIDA. AIDS 1997, 11:F101-5.

16. Mole L, Ockrim K, Holodniy M. Decreased medical expenditures for care of HIV-seropositive patients. The impact of highly active antiretroviral therapy at a US Veterans Affairs Medical Center. Pharmacoeconomics 1999, 16:307-15.

17. Bozzette SA, Joyce G, McCaffrey DF, Leibowitz AA, Morton SC, Berry SH, Rastegar A, Timberlake D, Shapiro MF, Goldman DP; HIV Cost and Services Utilization Study Consortium. Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy. N Engl J Med. 2001, 344:817-23.

18. Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, Beck EJ. Assessing the cost-effectiveness of HAART for adults with HIV in England. HIV Med. 2001, 2:52-8.

19. Stoll M, Claes C, Schulte E, Graf von der Schulenburg JM, Schmidt RE. Direct costs for the treatment of HIV infection in a German cohort after the introduction of HAART. Eur J Med Res. 2002, 7:463-71.

20. Keiser P, Nassar N, Kvanli MB, Turner D, Smith JW, Skiest D. Long-term impact of highly active antiretroviral therapy on HIV-related health care costs. J Acquir Immune Defic Syndr. 2001, 27:14-9.

21. Garattini L, Tediosi F, Di Cintio E, Yin D, Parazzini F; Gruppo di Studio ARCA (AIDS Resources and Costs Analysis). Resource utilization and hospital cost of HIV/AIDS care in Italy in the era of highly active antiretroviral therapy. AIDS Care 2001, 13:733-41.

22. Tramarin A, Postma MJ, Gerzeli S, Campostrini S, Starace F. The clinical and economic efficacy of HAART: a shift from in-patient medical to out-patient pharmaceutical care for HIV/AIDS patients in North-eastern Italy. AIDS Care. 2004, 16:213-218

23. Krentz HB, Auld MC, Gill MJ; HIV Economic Study Group. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. CMAJ. 2003, 169:106-10.

24. Lundgren JD, Mocroft A, Gatell JM, Ledergerber B, D'Arminio Monforte A, Hermans P, Goebel FD, Blaxhult A, Kirk O, Phillips AN; EuroSIDA Study Group. A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study. J Infect Dis. 2002, 185:178-87. Erratum in: J Infect Dis 2002, 186:145.

25. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, Costagliola D, D'Arminio Monforte A, De Wolf F, Reiss P, Lundgren JD, Justice AC, Staszewski S, Leport C, Hogg RS, Sabin CA, Gill MJ, Salzberger B, Sterne JA; ART Cohort Collaboration. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002, 360:119-29. Erratum in: Lancet 2002, 360:1178.

26. Van Sighem AI, Van de Wiel MA, Ghani AC, Jambroes M, Reiss P, Gyssens IC, Brinkman K, Lange JM, De Wolf F; ATHENA Cohort Study Group. Mortality and progression to AIDS after starting highly active antiretroviral therapy. AIDS 2003, 17:2227-36.

Scientific output 2003

Scientific output 2003

Articles in Journals

Chene G, Sterne JA, May M, Costagliola D, Ledergerber B, Phillips AN, Dabis F, Lundgren J, D'Arminio Monforte A, De Wolf F, Hogg R, Reiss P, Justice A, Leport C, Staszewski S, Gill J, Fatkenheuer G, Egger ME; Antiretroviral Therapy Cohort Collaboration. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet 362 (9385): 679-86, 2003.

Van Sighem AI, Van de Wiel MA, Ghani AC, Jambroes, Marielle, Reiss Peter, Gyssens IC, Brinkman K, Lange JMA, De Wolf F, on behalf of the ATHENA cohort study group. Mortality and progression to AIDS after starting highly active antiretroviral therapy. AIDS 17(15):2227-2236, 2003.

Friss-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiebaut R, Morfeldt L, De Wit S, Pradier C, Calvo G, Law MG, Kirk O, Phillips AN, Lundgren JD; Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 349 (21):1993-2003, 2003.

Burger D, Hugen P, Reiss P, Gyssens I, Schneider M, Kroon F, Schreij G, Brinkman K, Richter C, Prins J, Aarnoutse R, Lange JM; ATHENA Cohort Study Group. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. AIDS 17 (8): 1157-65, 2003.

Burger DM, Hugen PW, Aarnoutse RE, Hoetelmans RM, Jambroes M, Nieuwkerk PT, Schreij G, Schneider MM, van der Ende ME, Lange JM; ATHENA Study Group. Treatment failure of nelfinavir-containing triple therapy can largely be explained by low nelfinavir plasma concentrations. Ther Drug Monitor. 25 (1): 73-80, 2003.

Van der Ende ME, Prins JM, Brinkman K, Keuter M, Veenstra J, Danner SA, Niesters HG, Osterhaus AD, Schutten M. Clinical, immunological and virological response to different antiretroviral regimens in a cohort of HIV-2-infected patients. AIDS 17 (3): S55-61, 2003.

Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, Knysz B, Dietrich M, Phillips AN, Lundgren JD; EuroSIDA study group. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 362(9377): 22-9, 2003.

Mocroft A, Ruiz L, Reiss P, Ledergerber B, Katlama C, Lazzarin A, Goebel FD, Phillips AN, Clotet B, Lundgren JD; EuroSIDA study group. Virological rebound after suppression on highly active antiretroviral therapy. AIDS 17 (12): 1741-51, 2003.

Op de Coul ELM, Van de Laar MJW, Van Valkengoed IGM, Van Sighem AI, De Wolf F. Toenemend aantal allochtonen met HIV. HIV en aids in Nederland, 1 december 2003. Infectieziekten Bulletin jaargang 14, nummer 12, 2003 (pagina 412-413).

Reports

Gras LAJ, Van Sighem AI, van Valkengoed IGM, De Wolf F for the Dutch Collaborative HIV treatment Centres. Monitoring of Human Immunodeficiency Virus type 1 (HIV-1) in the Netherlands. November 2003, HIV Monitoring Foundation, Amsterdam, The Netherlands.

Op de Coul ELM, Van Valkengoed IGM, Van Sighem AI, De Wolf F, Van de Laar MJW. HIV en AIDS in Nederland. December 2003, Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven, The Netherlands.

Lectures

Gras LAJ. Preliminary results of a comparison of the long term effect of various antiretroviral therapies on CD4 cell counts. Afdeling Humane Retrovirologie AMC. 17 april 2003.

Gras LAJ. Preliminary results of a comparison of the long term effect of various antiretroviral therapies on CD4 cell counts. NATEC, Amsterdam. 27 april 2003.

Gras LAJ. Predicting the long term slope of CD4+T cell counts for different highly active antiretroviral therapies (HAART) in therapy naïve patients'. 9th European AIDS Conference in Warschau. 27 oktober 2003.

Gras LAJ. HIV Monitoring in The Netherlands. Department of Infectious Diseases Epidemiology, Imperial College, London. 26 januari 2003.

Van Sighem AI. Protease inhibitor containing therapy as a driving force of HIV-1 evolution. 7th International Workshop on HIV Observational Databases, Fiuggi, Italy, 28-30 March 2003.

Van Sighem AI. Protease inhibitor containing therapy as a driving force of HIV-1 evolution. Afdeling Virologie, AMC, Amsterdam. 17 April 2003.

Van Sighem AI. Survival update. Werkgroep HIV/AIDS van het Verbond van Verzekeraars. 9 May 2003.

Van Sighem AI. Survival update. Werkgroep HIV/AIDS van het Verbond van Verzekeraars. 26 May 2003.

Van Sighem AI. Mortality after starting HAART. 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France, 13-16 July 2003.

Van Valkengoed IGM. Presentatie Monitoring van HIV in Nederland, rapport 2002. Afdeling Virologie, AMC, Amsterdam. 17 april 2003.

Van Valkengoed IGM. Epidemiological methods in practice. Cursus Epidemiologie UMC Utrecht. 22 april 2003.

Van Valkengoed IGM. Therapie interrupties bij patiënten met CD4+ T-cel counts >500 tijdens HAART. IATEC Amsterdam. 27 april 2003

HIV en AIDS in Nederland

Workshop bij de presentatie van het Rapport 2003 van de Stichting HIV Monitoring tijdens de Nationale HIV/SOA conferentie over de resultaten van het nationale HIV-monitoring programma, 1 december 2003.

- Mortaliteit van HIV in tijden van HAART: veranderingen in de epidemiologie van de infectie
  Ard van Sighem (Stichting HIV Monitoring, Amsterdam)
- HAART in Nederland: klinisch, virologisch en immunologisch effect van achtereenvolgende regiems;
  Irene van Valkengoed (Stichting HIV Monitoring, Amsterdam)
- HIV-resistentie: hoe ernstig is het?
  Suzanne Jurriaans (AMC, Amsterdam)
- Zo gewonnen, zo geronnen: kosten effectiviteit van anti-HIV behandeling
  Hans Bogaards (Stichting HIV Monitoring, Amsterdam)
- Hoe verder: Conclusies, aanbevelingen en discussie
  Frank de Wolf (Stichting HIV Monitoring, Amsterdam)

Abstracts/Posters

Friss-Møller N, Weber R, D'Arminio Monforte A, El-Sadr W, Reiss P, Dabis F, Morfeldt L, de Wit S, Calvo G, Law M, Kirk O, Sabin C, Lundgren JD. Exposure to HAART is associated with an increased risk of myocardial infarction: the DAD study. 10th conference on retroviruses and opportunistic infections. Boston, USA, 10-14 February 2003.

Sabin C, D'Arminio Monforte A, May M, Grabar S, Reiss P, Lundgren J, Justice A, Staszewski S, Leport C, Dabis F, Montaner JSG, Johnson M, Gill MJ, Fatkenheuer G, Egger M. The changing incidence of clinical AIDS events in 12,574 treatment-naïve patients starting HAART. 10 th conference on retroviruses and opportunistic infections. Boston, USA, 10-14 February 2003.

Sterne JAC, May M, Costagliola D, Pezzotti P, Ledergerber B, De Wolf F, Lundgren J, Fusco JS, Staszewski S, Raffi F, Hogg RS, Philips AN, Gill MJ, Fatkenheuer G, Chene G. Does it matter where you came from? Prognosis of patients starting potent therapy, according to initial response. 10th conference on retroviruses and opportunistic infections. Boston, USA, 10-14 February 2003.

Bezemer D, van der Hoek L, Back N, De Wolf F, Coutinho R, Prins J. No recent transmission of drug resistant HIV and non-B subtypes in the Amsterdam Cohort studies. 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France, 13-16 July 2003.

Ledergerber B, Lundgren JD, Fusco GP, Weber R, Wit F, Castelli F, Staszewski S, Hogg R, Walker AS, Petoumenos K, d'Arminio Monforte A, Mussini C, Lampe F, Gill MJ, Philips AN. Factors contributing to the success of ART following three class virological failure: The Plato Collaboration. 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France, 13-16 July 2003

Van Sighem A, Ghani A, Reiss P, Gyssens I, Brinkman K, Lange JM, Van Valkengoed, I, Gras L, De Wolf F. Mortality after starting highly active antiretroviral therapy. IAS Conf HIV Pathog Treat 2003 Jul 13-16;2nd: Abstract No. 89. Antiviral Therapy 2003; 8(Suppl. 1):S208 (Oral)

Nieuwkerk P, Oort FJ. Effect of study characteristics on the association between self-reported adherence to HAART and virologic response: a meta-analysis. 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France, 13-16 July 2003.

Van Valkengoed I, Pogány K, Gras L, Van Sighem A, Wit F, Prins J, Brinkman K, Kroon F, De Wolf F, for ATHENA Cohort Study Group. Therapy interruptions in patients with >5000 CD4+ T-cell counts whilst on HAART. 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France, 13-16 July 2003 (Poster)

Van Valkengoed IGM, Pogány K, Gras L, Van Sighem AI, Wit FW, Prins JM, Kroon FP, BrinkmanK, De Wolf F. for the ATHENA Cohort Study Group. Therapy interruptions in patients with CD4+ T-cell counts >500 while on HAART. Second International AIDS Society Conference on HIV Pathogenesis and Treatment, Paris, abstract 609, 2003. Antiviral Therapy 2003; 8(Suppl. 1):S208 (Poster)

Ghani AG, Kwong G, Le Fevre AM, Gras L, Van Sighem A, De Wolf F, Anderson RM. Are those failing first-line HAART therapy containing Nelfinavir less likely to fail second-line PI-containing HAART? 9th European Aids Conference (Eacs), Warsaw, Poland, 25-29 October 2003.

Gras L, Van de Wiel MA, Van Valkengoed I, Van Sighem A, Ghani AC, De Wolf F for the ATHENA observational cohort. Predicting the long term slope of cd4+t-cell counts for different highly active antiretroviral therapies (haart) in therapy naïve patients. 9th European Aids Conference (EACS), Warsaw, Poland, 25-29 October 2003.

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