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The Curaçao Cohort Studies

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Chapter four

High incidence of intermittent care in HIV-1 infected patients in Curaçao before and after starting cART

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Abstract

Retention in care is one of the major challenges to scaling up and maximizing the effectiveness of combination antiretroviral therapy (cART). High attrition rates have been reported in the Caribbean region varying from 6% to 23%. We studied the incidence of and risk factors for intermittent care in a cohort of adult HIV-1 positive patients, who entered into care in Curaçao between January 2005 and July 2009. A total of 214 therapy-naïve HIV-1 infected patients aged 15 years or older, entered HIV care between January 2005 and July 2009. Intermittent care was defined as at least one period of 365 days or longer in which there was no HIV care contact in Curaçao. Cox regression models were used to identify characteristics associated with time to intermittent care. In all, 203 (95%) patients could be classified as having intermittent or continuous care. The incidence of intermittent care before starting cART was 25.4 per 100 person years observation (PYO), whilst 6.1 per 100 PYO after starting cART. Being born outside Curaçao was associated with intermittent care before and after starting cART. Time from diagnosis to entry into care was an independent predictor for intermittent care before starting cART. Younger age was independently associated with intermittent care after starting cART. Half of the patients returned to care after intermitting care. Upon returning to care, median CD4 count was 264 cells/mm^3 (IQR, 189-401) for those who intermitted care before starting cART, and 146 cells/mm^3 (IQR, 73-436) in those who intermitted care after starting cART. In conclusion, the incidence of intermitting care is high in Curaçao, especially before starting cART, and intermitting care before starting cART is an independent predictor for starting cART late.

Introduction

Retention in care and sustaining life long combination antiretroviral therapy (cART) are major challenges in scaling up and maximizing the effectiveness of cART. Previous studies showed that interruption of HIV care increases the risk of HIV disease progression and death for individual patients.[1,2] Before starting cART, retention in care is of increasing importance since current guidelines recommend initiation of cART based upon the monitoring of CD4 counts rather than clinical symptoms.[3,4] In addition, patients can be counseled on living a healthy lifestyle and preventing forward transmission and monitored for co-morbidities. After starting cART, continuous care is important for monitoring the effect of cART, identifying adverse events, ensuring continuous access to medication and motivating patients to remain compliant. Treatment interruption causes HIV infection to progress and is associated with poor prognosis[5] and increases the risk of the development of resistance.[6] Since cART has been shown to limit the probability of HIV transmission[7-18], treatment interruption could also increase the spread of HIV.[19]

Studies on the outcome of cART display varying rates of retention in HIV-1 infected patients in the Caribbean.[20-25] However, no data has been published on patient characteristics associated with intermittent care and only limited data are available on intermitting pre-cART care in a Caribbean setting. To achieve insight into when and why HIV-1 infected patients in a Caribbean island discontinue HIV care, we analyzed the incidence of and risk factors for intermittent care in a cohort of adult HIV-1 positive patients before and after starting cART in Curaçao. Curaçao is part of the Dutch Caribbean and is situated in the Southern Caribbean Sea. Currently, it has approximately 140,000 inhabitants and an estimated HIV prevalence of 0.61% to 1.05%.[26] In Curaçao, cART has been available since 1996. HIV patients are seen at the outpatient clinic of the St Elisabeth Hospital in Willemstad at intended intervals of 12 weeks. The hospital pharmacy is the sole distributer of antiretroviral drugs. Registration and monitoring of HIV infected individuals treated in Curaçao began in January 2005, in collaboration with the Dutch HIV Monitoring Foundation (Stichting HIV Monitoring [SHM]).[27]

Methods

The cohort of patients in Curaçao has been described in depth elsewhere.[20] We conducted a retrospective analysis of all HIV-1 infected patients older than 15 years who were therapy-naïve and entered care by visiting the HIV clinic for the first time between January 2005 and July 2009.

Continuous and intermittent care

A HIV care contact was defined as any visit to the outpatient or inpatient HIV clinic, any measurement of CD4 T-cell count or HIV viral load. Patients were classified as having intermittent care if they had at least one period of 365 days or longer in which they had no HIV care contacts and were not known to be receiving HIV-related care outside Curaçao or to have died or emigrated in this period. Patients who were known to have died within 365 days of their last contact or who were known to be receiving HIV care outside Curaçao and whose care was transferred within 365 days of their last HIV care contact in Curaçao were classified as having continuous care.

Classifying patients who are lost to follow-up

We attempted to trace the patients who were lost to follow-up in order to ascertain their vital status and consequently be able to classify them as having intermittent or continuous care. We first attempted to trace patients using contact information collected at clinical enrollment. If we could not contact the patient, or a contact person, we reviewed the national death registry. There were 38 patients who were lost to follow-up as of 1 July 2010; who had no HIV care contact between 1st July 2009 and 1st July 2010. Four patients of those who were lost to follow-up were traced to have died within 365 days of their last visit, and thus were classified as having continuous care. Twenty-five patients were classified as having intermittent care as 24 were traced to be alive and one had died more than 365 days after their last HIV care. Nine patients could not be classified as having continuous or intermittent care. Of these, five were traced to have emigrated but no additional data on their vital status were available and four could not be traced.

Definitions and statistical analysis

We defined cART as at least two nucleoside reverse transcriptase inhibitors combined with at least one protease inhibitor and/or non-nucleoside reverse transcriptase inhibitor or at least three nucleoside reverse transcriptase inhibitors including abacavir or tenofovir. When describing patients' clinical outcomes, we considered an acquired immunodeficiency syndrome (AIDS) defining illness starting less than two months after entry into care or returning after intermittent care. We defined patients as having advanced HIV disease if their CD4 T-cell count was less than 200 cells/mm^3 or they had AIDS.

We examined differences between groups of patients using Chi-squared tests for categorical variables and Mann-Whitney U tests for continuous variables. We used Wilcoxon signed rank tests in order to calculate differences in patients' health status before intermittent care and upon returning to care. We used Cox regression to examine univariate relationships between the time to the start of a first care break and gender, age at entry, country of birth, transmission

risk group, CD4 count at entry into care and start of combination anti-retroviral therapy. We included variables with a univariate p-value of 0.05 or less in a backwards stepwise procedure and excluded variables with a p-value of 0.05 or less from the model to obtain a multivariate model.

We calculated the incidence of intermitting care per 100 years of patient observation (PYO) by dividing the total number of patients who intermitted care by the number of patient years of observation. For pre-cART care, the start date of the observation time was the date of the first HIV care contact and the end date was the date that the patient started cART. If a patient did not start cART, the end date was the last visit date or the date of death for those who were alive or had died, respectively. For on-cART care, the start date of the observation time was the date, on which the patient started cART. The end date was the last visit date or the date of death for those who were alive or had died, respectively. We performed the statistical analysis using SPSS version 15.

Results

Of the 214 patients who entered care, 203 (95%) could be classified as having intermittent or continuous care. The vital status of 11 (5%) patients could not be ascertained during the period of discontinuous HIV care, and were excluded from the analysis. Of these, two had emigrated, five were traced to have emigrated and four could not be traced. The patients with unknown vital status were more likely to have been born outside Curaçao (8/11 versus 52/203, p-value = 0.002) and were younger (median 34 years (interquartile range [IQR], 26-42) versus 42 years (IQR, 34-49), p-value = 0.05) than the patients we could classify as having continuous or intermittent care.

Intermittent care before starting cART

Of the 203 patients who entered care and could be classified as having intermittent or continuous care, 165 (81%) had received pre-cART care. The characteristics of these patients are presented in Table 1. The total observation time for pre-cART care was 130 PYO, with a median of 16.9 weeks (IQR 3.6 – 62.8) per patient. In total, 37 patients (22%) intermitted care, resulting in an incidence of intermitting care of 28.5 per 100 PYO. The median time from entry to intermitting care was 14.3 weeks (95%confidence interval [CI] 5.6- 22.9 weeks). Six patients (16%) intermitted care directly after their first clinical visit.

Table 1: Baseline characteristics of HIV-1 infected individuals in Curaçao before and after starting combination anti-retroviral therapy (cART).

	Total included n=203		**Before cART** n=165		**After cART** n=148	
Male (n, %)	131	65%	114	69%	96	65%
Age at entry (median, IQR)	42	(34-49)	42	(34-48)	43	(35-51)
Born in Curacao (n, %)	147	72%	121	75%	108	74%
Heterosexual transmission (n, %)	147	72%	114	69%	106	73%
Pregnant at entry (n, %)*	8	4%	2	6%	8	5%
CD4count (cells/mm³) (median, IQR)	302	(105-472)	324	(134-487)	205	(68-344)
Unknown	63	31%	35	21%	47	32%
CD4 <200 cells/mm³ (n, %)	52	26%	42	32%	49	49%
AIDS (n, %)	13	6%	10	6%	11	7%
Time diagnosis-entry (weeks) (median, IQR)	14	(7-43)	15	(7-45)	13	(6-35)
Intermittent care (n, %)	56	28%	36	22%	20	14%

Legend Table 1: cART, combination antiretrorviral therapy; IQR, interquartile range; AIDS acquired immunodeficiency syndrome.
* Percentage of women of childbearing age (15-45 years)

The characteristics of patients with intermittent or continuous care before the start of cART are presented in Table 2. Patients, who intermitted care before starting cART, were more likely to be born outside Curaçao, younger and had higher CD4 counts at entry compared to pre-cART patients with continuous care. Although not significant, patients who intermitted care had a longer time between diagnosis and entry into care compared to those who continued care before starting cART. We present factors potentially associated with the time to intermittent care in Table 3. Being born outside Curaçao and a longer time between diagnosis and entry into care were independently associated with a shorter time to intermittent care.

Of the 37 patients who intermitted care, 22 (59%) spontaneously returned to care after a median duration of 1.74 years (IQR, 1.46-2.88). Upon returning to care, their median CD4 count (median 264 cells/mm^3, IQR 189-401) was lower than before they intermitted care (388, IQR 274-468, p=0.03). Of the patients whose disease stage could be determined, seven (41%) had advanced disease stage upon returning to care. Upon returning to care the median viral load was 4.4 Log HIV-RNA copies/ml (IQR, 4.2-4.8) and comparable to before intermitting care (4.2, IQR 3.9-4.8) p=0.73). Two patients (25% of the women aged 15 to 45 years) returned to care while pregnant.

Table 2: Baseline characteristics of HIV-1 infected individuals who intermitted care compared to those who had continuous care, before and after starting cART in Curaçao.

	Before cART					After starting cART				
	Continuous		Intermittent			Continuous		Intermittent		
	n=129		n=36		***p***	n=128		n=20		***p***
Male (n, %)	91	71%	23	64%	0.54	87	68%	9	45%	**0.04**
Age at entry (median, IQR)	42	(34-51)	38	(28-45)	**0.02**	44	(35-52)	38	(26-44)	**0.03**
Born in Curaçao (n, %)	99	79%	23	60%	**0.05**	99	79%	9	45%	**0.004**
Heterosexual transmission (n, %)	86	67%	28	80%	0.21	88	69%	18	95%	**0.02**
Pregnant at entry (n, %)*	2	10%	-	-	-	5	26%	3	38%	0.35
CD4count (cells/mm^3) (median, IQR)	297	(108-480)	399	(289-491)	**0.01**	205	(71-345)	205	(59-340)	0.63
Unknown	28	22%	7	19%		37	29%	10	50%	
CD4 <200 cells/mm^3 (n, %)	39	39%	3	10%	**0.02**	44	48%	5	50%	0.17
AIDS (n, %)	9	7%	1	3%	0.32	10	8%	1	5%	0.55
Time diagnosis-entry (weeks) (median, IQR)	14	(5-38)	22	(9-96)	0.07	12	(5-35)	28	(9-126)	0.17
Time between visits (weeks) (median, IQR)	12	(7-15)	22	(16-45)	**<0.001**	13	(11-15)	22	(13-46)	**0.001**
Returned to care (n, %)	-	-	22	61%		-	-	10	50%	

Legend Table 2: cART, combination antiretroviral therapy; IQR, interquartile range; AIDS, acquired immunodeficiency syndrome.
P-value based upon Fisher-exact test for categorical variables and Man Whitney-U test for continuous variables.
* Percentage of women of childbearing age (15-45 years)

Table 3: Factors predictive for a shorter time to intermittent care in HIV-1 infected individuals before and after starting combination antiretroviral therapy in Curaçao.

	Pre- cART						On-cART					
	Univariate			Multivariate			Univariate			Multivariate		
Variables	HR	95% CI	*p*	aHR	95% CI	*p*	HR	95% CI	*p*	aHR	95% CI	*p*
Age by ten years increase	0.86	0.65-1.14	0.29				**0.67**	**0.47-0.98**	**0.04**	**0.63**	**0.41-0.98**	**0.04**
Born in Curacao	**0.45**	**0.23-0.91**	**0.03**	**0.49**	**0.21-0.90**	**0.02**	**0.27**	**0.11-0.64**	**0.003**	**0.34**	**0.13-0.93**	**0.04**
Transmission risk group												
Hetero women	1						1			1		
Hetero men	0.89	0.42-1.88	0.75				0.65	0.27-1.67	0.37	1.34	0.46-3.96	0.59
MSM	0.46	0.18-1.16	0.10				**0.11**	**0.02-0.87**	**0.04**	0.19	0.02-1.52	0.12
Time diagnosis to entry (years)	**1.06**	**1.00-1.13**	**0.04**	**1.08**	**1.01-1.15**	**0.03**	1.05	0.98-1.13	0.20			
CD4 <200 cells/mm³ at entry												
No	1						1					
Yes	0.73	0.21-2.54	0.55				0.93	0.27-3.22	0.91			
Unknown	1.29	0.56-3.01	0.55				2.09	0.71-6.14	0.18			
Time entry to start (years)							0.62	0.24-1.56	0.31			
Pre-cART intermittent care							3.21	0.84-12.28	0.09			
CD4 <200 cells/mm³ at start												
No							1					
Yes							0.87	0.33-2.29	0.78			
Unknown							1.03	0.26-3.99	0.97			

Legend Table 3: cART, combination antiretroviral therapy; HR, hazard ratio; aHR, adjusted hazard ratio; MSM, men having sex with men; yrs, years; AIDS, acquired immunodeficiency syndrome.

It is remarkable that one patient had an undetectable viral load upon returning to care and for whose CD4 cell count had increased from 410 to 427 cells/mm^3. We suppose, but cannot prove, that this patient had received cART outside Curaçao. Fifteen (68%) patients initiated cART a median of 22 days (IQR, 15-269) days after returning to care. As of July 2010, none of the pre-cART patients, who intermitted care, had died.

Intermittent care after starting cART

Of the 214 patients who entered into care, 154 patients (72%) initiated cART of which 148 (96%) could be classified as having intermittent or continuous care. The characteristics of these patients are presented in Table 1. Median CD4 count at starting cART was 155 cells/mm^3 (IQR 63-243), 65% were male and median age at starting cART was 44 years (IQR, 35-52). Median follow-up after starting cART was 107 weeks (IQR 55-185). After starting cART, 20 patients (14%) intermitted care during 288 PYO, resulting in an incidence of intermittent care of 6.9 per 100PYO. Median time from starting cART to intermitting care was 2.7 years (95%CI 0.6- 4.8). Five patients (25%) intermitted care directly after starting cART.

Patients who intermitted care after starting cART, were younger compared to the patients with continuous on-cART care. Also, more patients were female and a higher proportion was born outside Curaçao in those who intermitted care compared with patients who had continuous care and a higher proportion was transmitted through heterosexual transmission. (Table 2) Factors independently associated with a shorter time to intermittent care after starting cART were younger age at entry and being born outside Curaçao. (Table 3)

Of the 20 patients who intermitted care after starting cART, 10 (50%) spontaneously returned to care after a median duration of 91.2 weeks (IQR 62.5-149.7). Median CD4 count before intermitting care was 215 cells/mm^3 (IQR 127-358) compared to 149 cells/mm^3 (IQR 73-436) after returning to care. Half of the patients returned to care in advanced disease stage. The median Log HIV-RNA plasma level before intermitting care was 4.0 copies/ml (IQR 2.5-5.3) and comparable to the median Log HIV-RNA plasma level upon returning to care (4.4, IQR 3.1-5.3). None of the patients who intermitted care had died after returning to care, one patient who intermitted had died during lost to follow-up for more than 365 days.

Discussion

We found a high incidence of intermitting care in an observational cohort of patients entering HIV care in Curaçao between 2005 and July 2009, especially in patients who had not started cART. Being born outside Curaçao was the main predictive factor for intermitting care both before and after starting cART. Other factors predictive for intermitting care were

time between diagnosis and entry in patients, who had not started cART, and younger age in patients, who had started cART. Half of the patients who intermitted care, returned to care, and had a more advanced HIV disease stage upon returning to care then when intermitting care.

Several observational studies describe retention in care[24,28-32] and the incidence of patients intermitting care varies considerably according to the definition used and the setting studied. A lower incidence rate of patients intermitting care has been found in European settings[2,28,29] than in our study. Studies carried out in Kenya[32] and French Guiana[33] reported higher incidence rates of patients intermitting care, comparable to these in our study. However conclusions should be drawn with caution, as the definitions of intermittent care used were different from ours. Despite the challenges in finding comparable studies, our study supports the findings of the Antiretroviral Treatment in Lower Income Countries (ART-LINC) study group, which reported higher rates of loss to follow-up among participants from low-income rather than high-income countries.[34] A possible explanation for the high rate of intermittent care in Curaçao is the lack of human resources and the passive follow-up of patients who intermit care.

In our study we found that patients had a higher risk of intermitting care before than after starting cART, supporting findings in European and African settings.[2,23,29,32,35-37] We observed a higher median CD4 count at entry in patients, who intermitted care, than in those who had continuous care before starting cART. This is also consistent with previous reports.[23,28,31,32,38] It may be possible to explain these findings by the fact that these patients have few observable symptoms and, thus, do not perceive the benefit of regular clinical follow-up. One of the main goals of retaining patients in care before starting cART is the monitoring of disease progression in order to ensure that the patient can start cART on time. We previously reported that a high proportion of patients in Curaçao started cART with CD4 cell counts under 200 cells/mm^3 or clinical AIDS.[20]

In this study, we showed that a longer time between diagnosis and entry into care was associated with an increased risk of intermitting care before starting cART, which supports the results of a previous study, which reported a delayed start of cART as a result of delayed entry into care.[39] Barriers for contacting the HIV care system after diagnosis are probably similar or still present during pre-cART care. Another possible explanation can be that without any observable symptoms, patients might not perceive the need to have regular follow-up or the utility of visiting a clinician and thus delay entry after diagnosis. Physicians should be aware of this when planning the start of cART in patients who had inefficient linkage to care because these patients are at increased risk of intermitting care before starting cART.

Patients who were born outside Curaçao were at increased risk of intermitting care, which supports international studies indicating non-indigenous patient groups to be at higher risk of intermitting care.[24,28-32] People born outside Curaçao are frequently immigrants and may reside in Curaçao illegally. They may encounter linguistic, economic and insurance problems and try to avoid contact with the local authorities, including health services, to avoid expulsion. However, we have no data on behavioral, economic and social factors that may have contributed to the risk of intermittent care. We also found that younger patients were more likely to intermit care after starting cART. This is consistent with the literature.[24,28-32,40] In French Guiana, less acceptance of the disease in younger age groups compared to older age groups and greater geographical and social instability were given as the main reason for younger patients intermitting care.[33] The risk of intermittent care in young patients is of particular concern, as young people are more often involved in risky sexual behavior and, potentially, fuel the HIV epidemic.

This study showed that the majority of patients who had started cART and intermitted care had plasma viral load levels > 1000 copies HIV-RNA /ml before intermitting care. Few other studies have observed high viral loads to be predictive for intermitting care.[31,41] A possible explanation could be that patients who do not adhere to cART are at higher risk of not adhering to clinical visits, and thus intermitting care. Viral loads >1000 copies/ml before and after intermitting care, indicate high infectiousness of those who intermitted care. People who intermit care cannot benefit from care, including interventions aimed at reducing forward transmission and therefor are probably contributing substantially to the epidemic. Limiting the number of patients who intermit care, is therefore necessary, to optimize treatment results and reduce forward transmission. As small Caribbean islands are forced to focus their prevention interventions due to the lack of human resources, data of this study can be used to develop an effective HIV prevention response by reducing the number of HIV-1 infected individuals who intermit care.

Intermittent care increases the risk of infecting others and increases the risk of adverse clinical outcomes for individual patients. In our study, half of the patients with intermittent care, returned to care which is higher than in Europe[29] and comparable to Northern France.[2] Upon returning to care a high proportion of patients had progressed to advanced disease stage and was in need of cART. This was also shown by Ndiaye et al. who reported a 5 time increased mortality risk in those who intermitted care.[2] In our study none of the patients who returned to care had died at the moment of analysis and only one patient who intermitted care had died, mortality could therefore not be assessed.

Due to the non cross-sectional methodology of the study, we prevented selection bias and under-estimation of intermittent care. By providing an incidence measure of intermitting care a more accurate measure for intermitting care was given compared to a percentage. Also, we traced those who were lost to follow-up in order to prevent misclassification of those who died while having continuous care resulting in an overestimation of intermitting care. However, our analysis has several limitations, as the number of patients was rather small, statistical power of the analysis was therefor limited. Also, as the observation period of the cohort was rather short, and the interval of intermitting care rather long, mortality in those who intermitted care could not be observed and the lack of association between intermitting care before cART with intermitting care after starting cART could not be ascertained. Further, the patients excluded for this analysis had the same baseline characteristics as those predictive for intermitting care, and thereby would have supported our study results. These weaknesses should be addressed in future studies. However, we did include all HIV-1 infected patients who entered care from the moment the web-based monitoring system was implemented and traced almost all patients who were lost to follow-up, minimizing selection bias and misclassification.

Our results provide a detailed overview of the incidence of intermitting care of all HIV-1 infected individuals in a single Caribbean country and provides valuable information on predictive factors for intermitting care, which can help clinicians to prevent intermitting care in their patient populations and which may help policymakers to set up effective prevention programs.

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