Chapter eight

General Discussion
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Treatment with combination antiretroviral therapy (cART) suppresses the HIV RNA concentration in plasma to very low levels in a large majority of HIV-infected patients thereby reducing HIV-related morbidity and mortality. Moreover, successful cART reduces the probability to transmit the virus. However, loss of viral suppression and the development of drug resistance over time, in part due to suboptimal adherence to cART, are major concerns. In the Caribbean, access to cART has improved since 2002. However, there are limited data on the clinical follow-up of HIV-1 infected individuals treated in the Caribbean. This hampers the evaluation of virological and immunological responses to cART and makes it difficult to monitor the effects of life-long cART. In this thesis, a detailed description is provided of the HIV-1 epidemic and treatment of HIV-1 infected individuals in Curaçao, a small island in the Caribbean and member of the Kingdom of the Netherlands. The immunological, virological and clinical responses to cART in HIV-1 infected individuals living in Curaçao are compared to those in Antillean, Surinam and Dutch individuals treated in the European part of the Netherlands. Late diagnosis and entry in to care are shown to be associated with a late start of cART. HIV-1 infected individuals living in Curaçao show high rates of intermittent care both before and after starting cART and high mortality rates are found in those who are lost to follow-up after starting cART. Based on the findings described in this thesis a new model is proposed for HIV care closely linking available primary health care with existing specialized HIV care in combination with monitoring of HIV care. As an example, quality indicators for such monitoring for the prevention of mother to child HIV-1 transmission in a Caribbean setting are described.

The immunological response to cART

In chapter 2, we analyzed the immunological, virological and clinical response to cART in HIV-1 infected individuals living in Curaçao. We compared their responses to cART with those of Antillean, Surinam and Dutch individuals treated in the Netherlands. We found less immunological recovery amongst HIV-1 infected individuals treated in Curaçao compared to patients groups in the Netherlands mainly as result of starting cART late in the course of infection. In chapter 3, we showed that late diagnosis and delayed entry in to care are associated with starting cART late. Hence, the suboptimal responses to cART may be due to individuals in Curaçao delaying the start of cART. Another explanation for a late start of cART would be lower initial CD4 cell count and more rapid decline amongst Antillean patients, since low CD4 cell counts at start of cART were found in both Antillean groups treated in Curaçao and the Netherlands. (Chapter 2) However, difference would imply a lower CD4 cell count amongst uninfected Antilleans compared to Dutch uninfected individuals. So far, there are no studies supporting such a difference.
Starting cART early in the course of HIV-1 infection improves clinical, immunological and virological outcomes.18-22 Until recently, initiation of cART was largely based on the monitoring of CD4 cell counts. Over time the threshold for starting cART has increased from 200 to 350 and then to 500 CD4 cells/mm³.23 The most recent guidelines recommend that individuals start cART straight after diagnosis, irrespective of their CD4 cell counts.24 This recommendation is based upon observational cohort data showing that all HIV-1 infected patients benefit from cART25 and a randomized clinical trial showing that cART reduces the likelihood of HIV-1 transmission and provides clinical benefits to HIV-1 infected individuals.4 In Curaçao between 1996 and 2007, HIV-1 infected individuals started cART when their CD4 cell counts declined to below 200 cells/mm³ or when individuals had clinical symptoms of AIDS. The reasons to do so were concerns about long-term adverse events and drug resistance following low adherence.26 From 2007 on cART was started according to Dutch guidelines and currently cART is given to infected individuals when CD4 cell counts drop to below 500 cells/mm³.27

**The virological response to cART**

In chapter 2 we observed a lower virological response over time in HIV-1 patients treated in Curaçao compared to those treated in the Netherlands. In addition to the late start of cART, differences in the drug regimens used and lower adherence rates may explain the lower virological response.28 Adherence rates measured by Real Time Medication Monitoring of all patients in Curaçao who started cART between October 2009 and November 2010 show correct pill intakes varying from 43%-78% during the first 6 months after starting cART.29 Analysis of the continuum of HIV care showed that at least one third of patients is lost between each single subsequent step of the cascade of care, resulting in a low overall proportion of viral suppression of only 24% of individuals newly diagnosed with HIV-1 infection. (Chapter 3) Rates of intermittent care before and after starting cART are high amongst HIV-1 infected individuals who entered care in Curaçao. (Chapter 4) Obviously, intermittent care before starting cART result in a delayed start of treatment. Intermittent care after start of cART may result in treatment interruptions causing progression of HIV infection30 and increasing the risk of developing resistance.31 Between 2008 and 2012 HIV drug resistance testing was performed in 158 patients who changed antiretroviral regimen because of virological failure. In total, 200 out of the 237 genotypic sequences were obtained of which 62% had high-level resistance to at least one antiretroviral drug. On the other hand, 31% of the sequences indicated full susceptibility to all drugs most likely, as a result of complete interruption of cART. However, resistance may reappear gradually after restarting cART.32 Since the Antillean HIV-1 infected individuals in the Netherlands show better virological response rates compared to those treated in Curaçao, region specific factors may explain the difference in sub-optimal adherence rates rather than population related factors.33,34 One
explanation for the high rate of intermittent care in Curaçao may be the lack of dedicated human resources and the passive follow-up of patients who intermit care. Other explanations are the transmission of drug resistant virus or recurrent HIV-1 infection. In Curaçao, resistance-associated mutations were detected in five of 62 patients who had a genotypic sequence within 1 year of diagnosis but before the start of treatment. To what extent recurrent HIV-1 transmission is contributing to lower virological response rates in HIV-1 infected patients in Curaçao is not known.

**The clinical response to cART**

In chapter 2 we observed comparable clinical response rates in Curaçao compared to HIV-1 populations treated in the Netherlands. However, since we found a higher lost to follow-up rate in the population treated in Curaçao compared to the Antillean population treated in the Netherlands, we assume there is a possible underreporting of death and AIDS defining illnesses. We analyzed the mortality rates in HIV-1 infected individuals after adjusting for those who were lost to follow-up (LTFU) and found higher mortality rates amongst those LTFU compared to patients who were on cART and continued HIV care. (Chapter 5)

In 2005, monitoring of HIV-1 infected individuals was initiated by the Red Cross Blood Bank Foundation in collaboration with HIV Monitoring Foundation (SHM, Amsterdam), the (outpatient) HIV clinic of the St Elisabeth Hospital and the Epidemiology & Research Department of Public Health services of the former Netherlands Antilles (GGD, Curaçao). Data were collected from written paper clinical files and stored online in the observational database of HIV monitoring Foundation in Amsterdam. Currently, clinical data are collected of all HIV-1 infected patients who entered HIV care in Curaçao between January 2000 and January 2013. This observational HIV cohort is unique for the Caribbean region and of high importance in supporting HIV clinical care, research and health policies.

In general, an observational cohort may provide information of a ‘real world’ practice. It gives feedback of current clinical practice and information to test certain hypotheses or develop clinical trials. Further, cohort studies are useful when analyzing events in chronological order and can therefore be used to distinguish between cause and effect. Cohorts may be used to measure various outcome variables and the effect of each variable on the probability of developing the outcome of interest (relative risk). However, limitations of cohort data exist and specific for the setting of Curaçao a few limitations are noteworthy to mention in order to correctly interpret data and the results of future data analysis. The study setting in Curaçao is relatively small which limits statistical analysis in order to proving association with enough power. Therefor in a small setting, longer follow-up time will be necessary, however this will limit the dynamics of clinical evaluation and results in in higher costs and higher risk of loss to follow-up. (Chapter 7)
Also, specific for the setting of Curaçao, challenges in ascertaining the quality of data exist. Data collection in Curaçao is mainly based upon collecting non-computerized clinical data, for which data can easily be missed. The web-based, electronic datasystem of SHM requires special queries and an updated administration in order to register patients who are lost to follow-up and to monitor the quality of data. (Chapter 4/5) Special skills are needed to run these queries. Thereby quality assurance of the data is still dependent on support of SHM, the Netherlands.

Further, clinical cohorts tend to lack data on HIV-risk behavior and provide only incompletely sero-prevalence data in at risk populations. Behavioral data and sero-prevalence data are crucial for understanding local HIV-1 epidemics. Behavior and sero-prevalence data in most at risk populations in relatively small Caribbean settings are limited due to the high fear of stigmatization as well as limitations of small sample sizes. Like in other relatively small Caribbean countries, Curaçao faces challenges in retrieving these data in order to describe and understand the local HIV-1 epidemic. Since the beginning of the HIV-1 epidemic the GGD of Curaçao has registered all newly HIV-1 infections confirmed by Western Blot techniques, however data on behavior are lacking. In addition, we suggest that data on risk behavior should be included in the observational clinical cohort and monitoring of HIV infection starting directly after diagnosis.

**Implications and future study: creating a new HIV care model**

Based upon the results of this thesis we suggest improving the effect of cART by developing a new HIV care model aimed at treating more individuals, earlier in their HIV-1 infection and providing lifelong viral suppression. Initiation of cART early in the course of infection requires a timely diagnosis of HIV-1 infection. In turn, timely diagnosis can be achieved only when those at risk for HIV are tested frequently. Timely and continuous viral suppression of HIV-1 infection impacts substantially on the chance of transmission of the virus. As most people in Curaçao access health care services through primary health care consisting of a relatively high number of well trained general practitioners, we suggest scaling-up HIV testing in general practitioners’ practice and starting cART immediately after diagnosis according to international guidelines. This would provide health benefits to HIV-1 infected individuals, by reducing morbidity and improving survival, and to the population as a whole, by reducing HIV-1 transmission. Adverse events has been shown to be very limited, as is the case for development of HIV-RNA resistance. Scaling-up HIV testing and starting cART immediately after diagnosis would result in tasks being shifted from specialized HIV care to general practitioners. We propose a model for this process of task shifting in Chapter 6.

Other reasons for tasks being shifted to primary health care exists. The last ten years HIV related care in Curaçao has been provided by the tremendous effort of one single health care worker, which puts strain on human resource capacity and sustainability of future HIV
care. HIV-1 infection has become a chronic disease, for which chronic, long-term HIV care is needed. For Curacao this implies that its substantial well-trained primary care capacity should become involved in the active, long-term follow-up and treatment of HIV-1 infected individuals. Further, involving general practitioners in HIV care could reduce stigma and fear, increases retention and reduces health care costs.48

Findings from research done in Australia show the increasing importance of the role of general practitioners49 and nurses50 when scaling up HIV testing and timely initiation of cART. Also, for the United States of America, the importance of incorporating primary health care in HIV care has been described.31 Decentralizing care to general practitioners is expected to result in better retention in care52,55 since it will bring care as close as possible to people’s homes. The WHO recommends task shifting to address human resource gaps and decentralizing cART to primary health care.23 Despite these recommendations, there is no consensus on how primary health care can best be integrated and there is no good evidence yet on the effectiveness of shared HIV care models.57-60 In Curacao, a pilot study will be launched introducing ‘test and treat’ in general practitioners practice, aimed at investigating the clinical effect of integrating HIV care services in primary health care setting. Next to the clinical effect, the public health care effect of integrating HIV care services in primary health care setting will be analyzed.

In conclusion, the response to treatment with cART in HIV-1 infected patients in Curacao is sub-optimal due to the late start of cART and low rates of retention in care. Given the results presented in this thesis, we propose maximizing the therapeutic effect of cART and introducing its preventive effect by focusing on early identification of HIV-1 infection followed by immediately starting cART and creating a HIV care continuum with intensive monitoring of life-long cART. Importantly, these strategies require integration of HIV care in the primary health care setting of Curacao resulting in tasks being shifted from specialized HIV care to general practitioners.
References


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