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Combination antiretroviral therapy (cART) has a dramatic impact on the morbidity and mortality of people living with human immunodeficiency virus type I (HIV-1). cART consists of at least three drugs from at least two classes of antiretroviral medications and has been available since 1996. The majority of people living with HIV-1 suppress virus production levels to below the quantification limit of standard RNA assays (less than 50 copies/ml) within 24 weeks after starting cART and achieve continuous suppression for up to eight years. People, who achieve viral suppression after starting cART, experience an increase in CD4 cell counts, indicating immune restoration and a substantially lower risk of dying than people who do not achieve viral suppression. In addition, viral suppression reduces the risk of HIV-1 transmission. Given that HIV-1 infected individuals currently need to take cART lifelong and that HIV-1 RNA can develop resistance to antiretroviral drugs, cART poses formidable challenges for HIV-1 infected individuals and the health care systems of their countries.

Access to cART has improved dramatically in the last decade in low and middle income countries. At the end of 2012, about ten million people were receiving cART worldwide. This represents a twenty-five-fold increase in ten years. Although late presentation and retention in care remain important challenges, the majority of reports show successful long-term viral, immunological, and clinical responses to cART in low and middle income countries. 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. By the end of 2009, 48% of patients with a CD4 cell count lower than 350 cells/mm³ were receiving cART, compared to 1% in 2004. 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.

The HIV-1 epidemic and antiretroviral treatment in the Caribbean

The Pan American Health Organization and the World Health Organization define the Caribbean as 28 islands and Mid and South American continental countries with culture and heritage linked to the islands. (Figure 1) The Caribbean is an extraordinarily diverse region. It is home to approximately 40 million people and it includes English, French, Spanish and Dutch speaking nations and territories of vastly different sizes. Although the World Bank, classifies most Caribbean countries as upper-middle income or high income countries, the majority of islands share similar sustainable development challenges, and are therefore called small island development states.
Figure 1: Caribbean region, black arrow indicating Curaçao.
In 1981, the first cases of Acquired Immune Deficiency Syndrome (AIDS) in the Caribbean were reported in Haiti in 1981. Cases of AIDS had also been reported among Haitians living in the United States of America at that time. However, retrospective analysis of patients affected by Kaposi’s sarcoma in Haiti showed that the first cases of AIDS in the region had actually been documented in 1979. In 1982, people with AIDS were reported in Jamaica and Bermuda. By 1987, all Caribbean countries had reported at least one case of AIDS. Current estimates suggest that 1% of adults in the Caribbean are living with HIV-1. This means that a total of 230,000 people in the region are infected with HIV-1, a figure that has remained stable during the last decade. However, the prevalence of HIV-1 varies considerably in the region. Cuba reports a prevalence of 0.1%, while the Bahamas reports one of 3.1%. As in Europe and the United States of America, the predominant HIV-1 subtype is subtype B. Although the first cases of HIV-1 were reported in men who have sex with men, heterosexual contact is currently thought to be the primary mode of transmission in the Caribbean.

Since 2002, access to antiretroviral therapy in the Caribbean has improved which resulted in a drop of number of AIDS cases. AIDS mortality dropped from 18,000 in 2001 to 10,000 in 2011. The first reports on the virological and immunological outcome of cART in HIV-1 infected patients treated in Caribbean setting showed successful virological response rates (serum HIV-1 RNA reduced to below 50 copies/ml) one year after starting cART in 2002 in Barbados, with a median increase of CD4 cell count of 165 cells/mm$^3$. In Haiti, a median CD4 cell count increase of 163 cells/mm$^3$ after 12 months of treatment was observed in the first 1004 HIV-1 infected patients starting cART in 2002. Amongst HIV-1 infected persons starting cART in 2004 in Kingston, Jamaica, the average increase in CD4 cell count 367 days after initiation of cART was 102 CD4 cells/mm$^3$. A concise and recent overview of virological and immunological responses to cART in Caribbean HIV-1 infected populations is currently lacking mostly because of the lack of accurate monitoring strategies and the high diversity in which Caribbean countries are organizing their HIV related care.

Despite the advanced gains following the introduction of cART, the Caribbean Epidemiology Centre (CAREC) reported that AIDS related illnesses were the fourth leading cause of death among Caribbean women and fifth among Caribbean men in 2007. In 2008, 15 Caribbean countries reported the survival rate one year after starting cART, with eight countries below 90% rate, the minimum acceptable level according to international standards. Higher mortality rates in HIV-1 infected patients who started cART in the Caribbean were associated with late clinical presentation whilst already being in advanced disease stage.
The HIV-1 epidemic and antiretroviral treatment in Curaçao

Curaçao is a Caribbean island in the Leeward Antilles in the southern Caribbean Sea. (Figure 1) The island is an autonomous part of the Kingdom of the Netherlands and, as such, does not appear in the Caribbean statistics of the Joint United Nations Program on HIV/AIDS. The island has an area of 444km² and has a population of approximately 150,000. (Figure 2) There are 2,000 live births each year and one third of the population is younger than 25 years of age. (Figure 3) Around 5,000 people immigrate to Curaçao annually, of whom 70% come from the European part of Netherlands.43

Figure 2: Map of Curaçao

The first cases of AIDS in Curaçao were reported in 1985 by the National AIDS Commission and consisted of one 27 year old male born in Curaçao, two women aged 31 and 50 years born in Colombia and Haiti and one ten month old baby girl, whose mother was born and tested positive for HIV in Curaçao. Three of these individuals died within a year of diagnosis. Between 1985 and December 2010, a total of 1426 individuals were diagnosed with HIV-
1 infection. Based upon data of the Epidemiology and Research department of the Public Health Department of Curaçao the prevalence of HIV-1 infection in the general population is estimated to be 0.62-1.05% and 1.03-1.72% in people aged between 15 and 49 years.\(^44\) However, there is currently no formal HIV surveillance system in Curaçao and, as in many other Caribbean countries, HIV surveillance data are limited.\(^38,45\) Epidemiological data on HIV-1 infections are based upon positive confirmatory testing for HIV-1 and only gender and the date of and age at testing are recorded. Over the last ten years the HIV-1 epidemic has stabilized with approximately 70 new diagnoses per year, the majority (64%) of which are in people aged between 25 and 44 years. The incidence of HIV infection for females and males per 1000 population in Curaçao between 2000 and 2007 were estimated to be approximately 0.6 per 1000 for men and 0.4 per 1000 per women.\(^44\)

**Figure 3:** Distribution of age in Curaçao, with males shown on the left and females on the right.\(^43\)

![Figure 3](image)

**Legend figure 3:** The population is distributed along the horizontal axis, with males on the left and females on the right. The male and female populations are broken down into 5-year age groups represented as horizontal bars along the vertical axis, with the youngest age groups at the bottom and the oldest at the top.

Epidemiological and clinical data suggest that the HIV-1 epidemic in Curaçao started amongst men who have sex with men but subsequently shifted to heterosexual transmission.\(^44,46\) Little is known about behavioral factors facilitating the HIV-1 epidemic in Curaçao. However, a number of issues have been identified. These include: inconsistent condom use; sexual promiscuity in small networks; concurrent partnering; machismo; stigmatization of sexual diversity, such as men who have sex with men; a matri-focus family system; prostitution and transitional sex; a lack of sexual knowledge; and regular vaginal lavage.\(^47-49\)
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The St Elisabeth Hospital (SEHOS) provides health care and treatment services for all HIV infected individuals in Curaçao and one medical specialist treats the majority of them. General practitioners refer people with newly diagnosed HIV infection to this specialist. Mono- and duo-antiretroviral therapy was available to inpatients with advanced disease before 1996. cART has been available since 1996 and is provided via the hospital pharmacy. Costs for HIV treatment are covered by national health insurance for more than 80% of individuals. However, each year, one to three HIV-1 infected individuals report being uninsured. Antiviral medication may be unaffordable for them.50

In 2005, the Red Cross Blood Bank Foundation, Curaçao, in collaboration with Stichting HIV Monitoring, Amsterdam, the SEHOS, Curaçao and the Epidemiology and Research department of the Public Health Department of Curaçao initiated the monitoring of clinical follow-up and disease progression in HIV infected individuals receiving HIV related care. The first reports on the outcome of cART in HIV-1 infected patients, who started cART between 2001 and 2006, showed that HIV-1 positive individuals generally started cART later than recommended (median 119 CD4 cells/mm³) and that they had a suboptimal virological response after five years of treatment, with 58% of patients having 500 or less HIV-1 RNA copies per ml.51

Entry into HIV related care

Access to cART and starting cART prior to deterioration of CD4 cell counts below the level of 500 cells/mm³ is crucial for reaching a maximum therapeutic effect in the individual patient52-54, as well as preventing transmission of HIV.55 In the whole of the Caribbean, including Curaçao, late clinical presentation of HIV-1 infected individuals is a major hurdle for starting cART on time.56-58 Individuals may start cART later than optimal because of late diagnosis, delayed entry into HIV related care after diagnosis, or delayed initiation of cART after entry into care.

Intermittent care

Continuous suppression of HIV-1 is needed to prevent deterioration of the immune system and subsequently development of HIV-1 related disease and AIDS.59 Interruption of HIV related care increases the risk of HIV disease progression and death.60,61 Regular monitoring after HIV-1 diagnosis can help to determine when to start cART and can prevent unnoticed immune deterioration. After the start of cART, regular monitoring supports clinical follow-up. Individuals with HIV-1 need to remain in HIV related care, since interruption of cART is associated with disease progression,60 shorter survival, a higher risk of development of viral resistance to antiretroviral drugs,62,63 and increased risk of transmission to others.64 Varying retention rates have been reported in HIV-1 infected patient populations in the Caribbean.24,25,41,65-69 One of the first reports on the outcome of cART in HIV-1 infected patients in Curaçao showed that 10-20% of those who ever started cART were not using treatment after 2004.51
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Survival following HIV related care
In the general population of Curacao, the life expectancy at birth is 72.4 years for males and 80.1 years for females, while in 2011, the mortality rate was 8.5 per 1,000 inhabitants.43 The leading cause of death in the former Netherlands Antilles is cardio-vascular disease.70 National data on HIV/AIDS related mortality are available up to 2004 and the absolute number of deaths each year has declined since the introduction of cART in 1996.44 Between 1996 and 2008, 343 individuals were diagnosed with HIV-1 infection, of whom 310 (90.4%) were still alive in 2008.71 Mortality rates in HIV-1 infected individuals, who started cART between 1998 and 2004 in Caribbean countries, vary from 6% to 24%.41 This suggests that the mortality rate amongst HIV-1 infected individuals is in line with other countries in the region.

Researchers need insight into the vital status of individuals who have become lost to follow-up from treatment to evaluate the outcomes of antiretroviral treatment72, but often do not have access to this type of data. This is true for almost all Caribbean countries and hence survival outcomes of Caribbean cohorts of HIV-1 infected patients are estimated based upon results of African studies13,41 which leads to substantial uncertainty regarding the effect of cART on mortality in the Caribbean.

Quality of HIV related care
Combination antiretroviral therapy has improved significantly since its introduction in 1996. cART regimens have become simpler in terms of dosing, more effective and better tolerated.73-76 The survival of HIV-1 infected individuals has also improved dramatically since the introduction of cART. However, the life expectancy of HIV-1 infected people varies across populations and subgroups77 due to unequal access to care and variations in the quality of HIV related care. Quality of care can be defined in many ways, but the one proposed by the Committee on Quality of Health Care in America, Institute of Medicine has been widely accepted. This definition is “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”.78 Monitoring and evaluating the quality of care provided to HIV-1 infected individuals is important as this process can identify strategies to improve the quality of care and outcomes of cART.79 In order to optimize the effects of cART and to prevent the development of resistance to antiretroviral medications, recommendations have been formulated in national and international guidelines. In order to make a valid and reliable assessment of current practice of antiretroviral therapy in patients with HIV infection, key recommendations from these guidelines can be translated into measurable elements or “indicators”.80 In order to assess and improve the quality of ARVs used in a Caribbean setting a valid set of quality indicators is required. Above all, this set should be applicable in practice.
Outline of this thesis

In this thesis, we compare the clinical, virological and immunological outcomes of cART in HIV-1 infected individuals living in Curaçao with those of individuals living in the Netherlands (Chapter 2). We examine the relationship between the late diagnosis of HIV-1 infection and late entry into HIV related care with the late start of cART (Chapter 3). We studied the effect of individuals intermitting HIV-related care before and after starting cART (Chapter 4) and the impact of individuals becoming lost to follow-up on the reported outcomes of cART (Chapter 5). In addition, we surveyed health care workers perceptions on the current program of HIV related care in Curaçao and analyzed their needs for training if HIV related care were to be decentralized (Chapter 6). Furthermore, we developed quality of care indicators for the prevention of mother-to-child-HIV transmission and analyzed the applicability of quality of care indicators in Curaçao, Aruba and St Maarten (Chapter 7).
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