Impact of antiretroviral therapy on HIV-1 transmission dynamics

Bezemer, D.O.

Citation for published version (APA):
Summary

The first AIDS cases in the Netherlands were diagnosed in 1982 among men having sex with men (MSM). In 1984 serological testing was possible and from 1991 antiretroviral mono therapy was available. However resistant strains emerged within several weeks on therapy, and were also shown to be transmitted. Since 1996 effective combination antiretroviral therapy (cART) is available. cART proved effective as morbidity and mortality among HIV infected patients strongly decreased. cART reduces the viral load and therewith also the infectiousness. However annual HIV-1 diagnoses among MSM have been increasing over the past decade. We wanted to know the impact that cART has had on the transmission dynamics of HIV-1 among MSM. For this we used data till 2007 from the prospective Amsterdam Cohort Studies and 24 HIV treatment centres in the Netherlands as part of the ATHENA national observational cohort.

First we developed a mathematical HIV-1 transmission model including the distribution in disease progression and parameters on cART use and estimated the changes in risk behaviour and time from infection to diagnosis, needed to explain annual diagnoses of HIV-1 and AIDS. Herewith we could calculate the reproduction number $R(t)$, being the number a newly infected MSM at time $t$ will on average infect over his whole infectious lifespan if conditions remain the same as at time $t$: when larger then one the epidemic will increase, when smaller then one the epidemic will contract. We show that together with a 57% decrease in risk-behaviour $R(t)$ declined early on from initial values above two and was maintained below one from 1985 to 2000. Since 1996, when highly active antiretroviral therapy became widely used, the risk behaviour rate has increased 66%, resulting in an increase of $R(t)$ to around the threshold one for a self-sustaining epidemic in the latest period 2000 tot 2006. The percentage of the undiagnosed HIV positive MSM of the total number of infected MSM has decreased to 24%, but only so due to an increase in survival of the diagnosed population. In absolute numbers around 1600 HIV positive MSM were undiagnosed at the end of 2006, estimated to be responsible for 90% of new HIV-1 transmissions. Decreasing time from infection to diagnosis, 2.5 years on average in 2006, with subsequent cART can prevent thousands of future infections. The recent increase in the proportion of newly diagnosed individuals with high CD4 cell counts corroborates our model’s inferences in interpreting recent increases in annual number of new HIV-1 diagnosis as rising transmission and increased diagnosis rather than improved diagnosis of people infected many years in the past. If the risk behaviour would not have increased with the introduction of cART, $R(t)$ would be 0.60, and the epidemic would be in decline. Hypothetical scenario analysis further showed that in the absence of cART limiting infectiousness in treated patients, the epidemic could be more than twice as large as it is at present.

Next we wanted to obtain better insight in the time span from infection to onwards transmission. For that we performed a phylogenetic study of polymerase sequences isolated from 2877
HIV-1 subtype B infected patients. These RNA sequences are obtained as part of the screening for resistant strains to antiretroviral drugs, and their mutual similarities have proved valuable in reflecting the underlying transmission networks. Among MSM 25% of onward transmissions was estimated to occur within 7 months after infection, half of transmissions within 17 months, and 75% within 2.7 years. This finding is compatible with the results of the transmission model. Transmission of resistant strains from the cART treated population showed to be limited. But 23% of people failing cART, without previous monotherapy, were initially themselves infected with a resistant strain. Strains with stable resistance-related mutations in the absence of cART have formed sub-epidemics. On average 6% [95% confidence interval (CI), 3.8 – 8.7 %] of infections among MSM had drug-resistant mutations between 1987 – 2007. First after 2004, 1% of infections among MSM considered a multidrug resistant strain. The apparent pressure to mutate in the absence of cART at several resistance-associated positions confirms a decreased viral fitness of those mutations. Only when a sequence is obtained shortly after infection the presence of unstable mutations can be monitored.

In conclusion there is a resurgent epidemic amongst MSM. Increasing risk-behaviour has offset the benefits of cART in reducing HIV transmission in The Netherlands. HIV-1 among MSM spreads mostly from the undiagnosed population, and so do resistant strains. Transmission of multidrug resistance is rare. Early diagnosis should be achieved by contact tracing and improved and frequent rapid testing. Together with early access to cART and a decrease in risk behaviour this may effectively contain epidemic spread amongst MSM.