Sources of HIV-1 transmission in the ongoing, concentrated HIV epidemic among men having sex with men in the Netherlands between July 1996 and December 2010

Oliver Ratmann[1], Ard van Sighem[2], Daniela Bezemer[2], Alexandra Gavryushkina[3], Frank de Wolf[1], Peter Reiss[2], Christophe Fraser[1] and the ATHENA observational cohort

[1] Department of Infectious Disease Epidemiology, Imperial College London, United Kingdom; [2] HIV Monitoring Foundation, The Netherlands; [3] Department of Computer Science, University of Auckland, New Zealand

Contact: oliver.ratmann@imperial.ac.uk

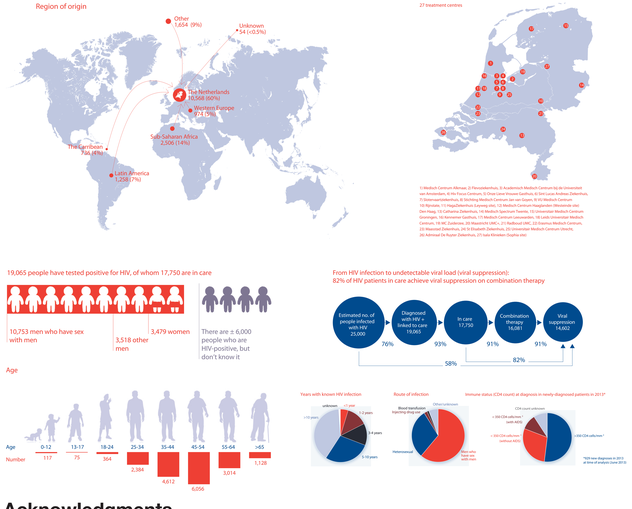
Imperial College London

HIV Monitoring

Summary and Conclusions

In the Netherlands, nearly all HIV infected MSM in care are enrolled in the open, national opt-out ATHENA cohort, and 46% of registered MSM have a viral sequence sampled. At this sequence coverage, large-scale phylogenetic linkage analyses enable a detailed quantification of the sources of HIV transmission. With this knowledge, the potential impact of components of a combination prevention package can be quantified. We compiled the internationally largest compendium of phylogenetically probable HIV transmission events amongst MSM. The estimated sources of onward transmission for the period 1996/07-2010/12 are detailed in table 1. Approximately two thirds of all HIV infections originate from undiagnosed men, and of those at least 41% (36%-45.7%) occured within the first year of HIV infection, in line with Ref 9. This limits the impact both testing for HIV and treatment as prevention could have in averting secondary HIV infections[8]. We estimated the fraction of HIV infections that could have been averted between 2009/07-2010/12 through various combination prevention approaches, which may guide future policy change under the assumption that sexual risk behaviour does not increase.[10] Results are described in figure 4.

Research in context: HIV in the Netherlands 2014



Acknowledgments

The ATHENA observational cohort has been made possible through the collaborative efforts of Academic Medical Center of the University of Amsterdam J.M. Prins, T.W. Kuijpers, H.J. Scherpbier, J.T.M. van der Meer, F.W.M.N. Wit, M.H. Godfried, P. Reiss, T. van der Poll, F.J.B. Nellen, J.M.A. Lange', S.E. Geerlings, M. van Vugt, D. Pajkrt, J.C. Bos, W.J. Wiersinga, M. van der Valk, A. Goorhuis, J.W. Hovius, J. van Eden, A. Henderiks, A.M.H. van Hes, M. Mutschelknaus, H.E. Nobel, F.J.J. Pijnappel, A.M. Westerman S. Jurriaans, N.K.T. Back, H.L. Zaaijer, B. Berkhout, M.T.E. Cornelissen, C.J. Schinkel, X.V. Thomas. Admiraal De Ruyter Ziekenhuis, Goes M. van den Berge, A. Stegeman, S. Blaas, L. Haga de Looff, D. Versteeg. Catharina Ziekenhuis, Eindhoven M.J.H. Pronk, H.S.M. Ammerlaan E.M.H.M. Korsten-Vorstermans, E.S. de Munnik A.R. Jansz, J. Tjhie, M.C.A. Wegdam, B. Deiman, V. Schamhorst. Emma Kinderziekenhuis A. van der Plas, A.M. Weijsenfeld. Erasmus Medisch Centrum, Rotterdam M.E. van der Ende, T.E.M.S. de Vries-Sluijs, E.C.M. van Gorp, C.A.M. Schurink, J.L. Nouwen, A. Verbon, B.J.A. Rijnders, H.I. Bax, R.J. Hassing, M. van der Feltz N. Bassant, J.E.A. van't Beek, M. Vriesde, L.M. van Zonneveld A. de Oude-Lubbers, H.J. van den Berg-Cameron, F.B. Bruinsma-Broekman, J. de Groot, M. de Zeeuw- de Man, M.J. Broekhoven-Kruijne M. Schutten, A.D.M.E. Osterhaus, C.A.B. Boucher. Erasmus Medisch Centrum-Sophia, Rotterdam G.J.A. Driessen, A.M.C. van Rossum, L.C. van der Knaap, E. Visser. Flevoziekenhuis, Almere J. Branger, C.J.H.M. Duijf-van de Ven. Haga Ziekenhuis, Den Haag E.F. Schippers, C. van Nieuwkoop, R.W. Brinkcordine J.M. van Lijoenen G. van der Hut P.P.H. Franck. HIV Focus Centrum (DC Klinieken) A. van der Valk, M. Bravenboer, J.W. Bouwhuis J.F. van den Berg, A.G.W. van Hulzen G.L. van der Bliek, P.C.J. Bor P. Bloembergen, M.J.H.M. Wolfhagen, G.J.H.M. Ruijs. Kennemer Gasthuis, Haarlem R.W.W. ten Kate, P. Soetekouw N. Hulshoff, L.M.M. van der Pol, M. Schoemaker N. Bermon W.A. van der Reijden, R. Jansen, B.L. Herpers, D.Veenendaal. Leids Universitair Medisch Centrum, Leiden F.P. Kroon, S.M. Arend, M.G.J. de Boer, M.P. Bauer, H. Jolink, A.M. Vollaard W. Dorama, C. Moons E.C.J. Claas, A.C.M. Kroes. Maasstad Ziekenhuis, Rotterdam J.G. den Hollander, K. Pogany M. Kastelijns, J.V. Smit, E. Smit, M. Bezemer, T. van Nieuwkerk O. Postmodi. Maastricht UMC+, Maastricht R.H. Lowie, A. Oude Lashof, D. Posthouwer, R.P. Ackens, J. Schippers, R. Vergoossen, B. Weijenberg Maes P.H.M. Heukkoul, I.H. Loo. MC Zuiderzee, Lelystad S. Wasse, R. El Moussaoui, M. Hetmulter, M. Hetmulter. Medisch Centrum Alkmaar W. Kortmann, G. van Twillert, J.W.T. Cohen Stuart, B.M.W. Diederen, D. Pronk, F.A. van Trulen-Oud, W. A. van der Reijden, R. Jansen. Medisch Centrum Haaglanden, Den Haag E.M.S. Leyten, L.B.S. Gelinck, A. van Hartingsveld, C. Meerkerk, G.S. Willebeest, J.A.E.M. Mutsaers, C.L. Jansen. Medisch Centrum Leeuwarden, Leeuwarden M.G.A.wan Vonderen, E.P.F. van Houte, K. Dilkstra, T. Schaar, J. Weel. Medisch Spectrum Twente, Enschede G.J. Kootstra, A.I.M. de Jong-van de Kassteele, J. Schouten, Annelies Verbon Gasthuis, Amsterdam A. Brinkman, P.H.J. Frissen, H.L. Blok, W.L. Out, C. Schouten, M.A. Roosma, F. Stolwijk, P. Schneeberger, A. Brouwers, J. Barendse, K. Koelewijn, M.J. Bosch, M.E. van der Mache, A.M.C. Wever. Onze Lieve Vrouwe Gasthuis, Amsterdam M. Prins, R.A. Kroon, J.M. Lange, A.S.Schneider, R. Schreij, M.E.W. Hemmer, A.S.Schneider, R. Schreij, P. Gringhuis, J.C. Grijsje-Huisman, B.J. Zorner, F.F. Stelma, D. Burger, Rijnstate, Arnhem C. Richter, J.P. van der Berg, E.H. Gisolf, G. ter Beest, P.H.M. van Bentum, N. Langebeek, R. Tamessen, C.M.A. Swanink, Sint Lucas Andreas Ziekenhuis, Amsterdam J. Veenstra, K.D. Lettinga M. Spelbrink, H. Sulman, M. Spelbrink, E. Witte, M. Damen, P.G.H. Peerbooms. Slotervaartziekenhuis, Amsterdam J.W. Mulder, S.M.E. Vrouwenrits, F.N. Lauw, M.C. van Broekhuizen, H. Paap, D.J. Vlasblom, E. Oudmaijer Sanders, P.H.M. Smits, A.W. Rooingh. Stichting Medisch Centrum Jan van Goyen, Amsterdam D.W.M. Verhagen, J. Gellings, St Elisabeth Ziekenhuis, Tilburg M.E.E. van Kasteren, A.E. Brouwer, B.A.F.M. de Kruijf-van de Wiel, M. Kuipers, R.M.W.J. Spanjerwels, B. van der Ven, J.H. Marcelis, A.G.M. Buiting, P.J. Kabel. Universitair Medisch Centrum Groningen, Groningen W.F.W. Bierman, H.G. Sprenger, E.H. Scholvinck, S. van Assen, K.R. Wiling, Y. Stienstra, H. de Groot-de Jonge, P.A. van der Meulen, D.A. de Weerd, H.G.M. Niesters, A. Riezebos-Brilman. Universitair Medisch Centrum Utrecht, Utrecht A.I.M. Hoepelman, M.M.E. Schneider, T. Mudrikova, P.M. Ellerbroek, J.J. Oosterheert, J.E. Arends, R.E. Barth, M.W.M. Wasserberg, D.W.M. van Elsland Lauritjsen, L.M. Laan, E.E.B. van Oers-Hazeltzet, J. Pattist, S. Vervoort H.E. Nieuwenhuis, R. Frauenfelder, R. Schuurman, F. Verduyn-Lunel, A.M.J. Wensing, VU Medisch Centrum, Amsterdam E.J.G. Peters, M.A. van Agtmael, R.M. Pierenboom, M. Bomers, J. de Vocht, L.J.M. Elsenburg, A.M. Petterson, C.M.J.E. Vandenbroucke-Grauls, C.W. Ang. Wilhelmina Kinderziekenhuis, UMCU, Utrecht S.P.M. Geelen, T.F.W. Wolfs, L.J. Bont, N. Nauta. Curacao: Sint Elisabeth Hospital, Willemstad C. Winkel, A. Durand, F. Muskiet, R. Voigt, I. van der Meer. Coordinating centre: S. Zaheri, M. Hillebregt, Y. Tong, V. Kimmel, M. Berkhout, R. van den Boogaard, S. Grivell, P. Hoekstra, A. Jansen, A. de Lang, B. Lascaris, M. van den Akker, Y. Bakker, D. Bergsma, M. Broekhuysen, E. Claessen, L. de Groot, A. de Jong, C. Lodewijk, R. Meijering, B. Pieck, M. Raithke, C. Rex, R. Regtop, Y. Ruja, M.J. Rademaker, L. Murjahnelli, E. Kruijne, M. School, E. Tuijn, L. Veenenberg, T. Wouddina, B. Tak, D.O. Bezemer, L.A.J. Gras, A.I. van Sighem, C. Smit.

Supported by wellcome trust

References

1. Beyrer, C., et. al. (2012). Global epidemiology of HIV infection in men who have sex with men. Lancet, 380(9839), 367-377.
2. Fisher, M., et. al., (2012). Determinants of HIV-1 transmission in men who have sex with men: a combined clinical, epidemiological and phylogenetic approach. AIDS, 24(1), 1739-1747.
3. Stamatakis, A., & Aberer, A. J. (2013). Novel Parallelization Schemes for Large-Scale Likelihood-based Phylogenetic Inference. Ieee 27th International Parallel and Distributed Processing Symposium (Ipdps 2013), 1195-1204
4. Vrancken, B., et. al. (2014). The Genealogical Population Dynamics of HIV-1 in a Large Transmission Chain: Bridging within and among Host Evolutionary Rates. Plos Computational Biology, 10(4).
5. Little, Roderick J. A., & Rubin, Donald B. (1987). Statistical analysis with missing data. New York ; Chichester: Wiley.
6. Das, M., et. al. (2010). Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One, 5(6), e11068.
7. Fogarty, A, et. al. (2006). The Health in Men and Positive Health cohorts: A comparison of trends in the health and sexual behaviour of HIV-negative and HIV-positive gay men, 2002-2005. National Centre in HIV Social Research, Sydney.
8. White, P. J. et. al. (2014). How Many HIV Infections may be averted by targeting primary infection in men who have sex with men? J Infect Dis, 210 Suppl 2, S594-599.
9. Volz, E., et. al. (2013). HIV-1 Transmission During Early Infection in Men Who Have Sex with Men: A Phylodynamic Analysis. PLoS Med
10. Jansen, et. al., (2011). Ongoing HIV-1 transmission among men who have sex with men in Amsterdam: a 25-year prospective cohort study. AIDS, 25(4), 493-501.

Background

The number of new HIV infections amongst men having sex with men (MSM) is increasing[1], despite the widespread availability of prevention services and of antiretroviral therapy (ART). Little guidance as to how to prioritize components of a combination prevention package is currently available.[1]

Objectives

- to reconstruct an evidence base of past HIV transmission events amongst MSM
- to estimate the proportion of HIV tranmissions originating from consecutive stages of HIV infection and care (figure 1)
- in light of the sources of transmission, to estimate the proportion of HIV infections that could be averted through specific components of a combination prevention approach

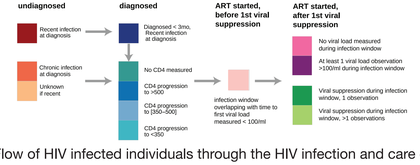


Figure 1. Flow of HIV infected individuals through the HIV infection and care continuum.

Methods

- We identified putative transmission events between recently infected MSM within their first year of HIV infection and their phylogenetically probable transmitters[2]. The viral phylogeny was reconstructed with maximum-likelihood methods[3]; %divergence cut-offs were not used to avoid exclusion bias; missed intermediates in pairs were excluded with a compatibility test[4].
- We used records in the national-opt out ATHENA cohort to determine the staging of probable transmitters within the infection and care continuum by six week intervals (figure 2).
- We adjusted for stage-specific sampling and censoring biases[5].
- In counterfactual scenarios, we re-distributed probable transmitters to less infectious stages in the HIV infection and care continuum according to specific intervention protocols.

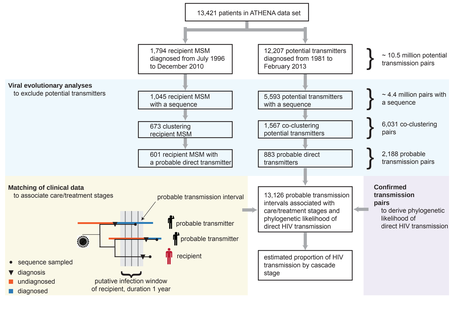


Figure 2. Methods flow chart.

Results

- We found 883 phylogenetically probable transmitters to 601 recipient MSM with an average of 3.6 (maximum 17) probable transmitters per recipient in 2,188 pairs. We expected to find 520 recipient MSM whose transmitters are sampled, indicating that exclusion criteria did not induce exclusion bias.
- We observed 1,641 person-years of probable transmission intervals and expect that a further 2,008 person-years are missing after adjusting for stage-specific sampling biases (figure 3).
- Individual phylogenetic transmission probabilities were small (mean: 4.8%, interquartile range 0.4%-7.1%). When grouped by infection/care stage, these transmission probabilities were highly informative as to how transmission rates change with progression through the HIV infection and care continuum (figure 3).
- The estimated proportion of HIV transmission originating from each of thirteen stages in the HIV infection/care continuum are given in table 1. These imply that viral suppression induced by ART is highly effective in preventing transmissions amongst MSM (figure 4).
- The absence of a reduction in HIV incidence amongst MSM despite substantial increases in ART provision may be explained by an increasing number of diagnosed but untreated men since 2000. The only subgroup that declinded markedly was that of diagnosed but untreated men with a CD4 count below 350 cells/mm3, and we found that the proportion of transmissions originating from this group also declined markedly (figure 4).
- 23% of all MSM diagnosed between 09/07-10/12 had a last negative test within 12 months prior to diagnosis. If 70% had been tested as reported for San Francisco[6] or Australia[7] and ART had been provided immediately, we estimate that a third of all HIV infections between 09/07-10/12 could have been averted (figure 4).
- The impact of test and treat is limited by the large proportion of transmissions that occur within the first 12 months of HIV infection amongst MSM[8]. Primary HIV prevention strategies circumvent the operational problem of identifying infected men immediately after infection. If 50% of all uninfected men had taken daily, tenofovir-based oral pre-exposure prophylaxis, 50% of all men had been tested every 12 months and ART had been provided immediately, we estimate that half of all HIV infections between 09/07-10/12 could have been averted (figure 4).

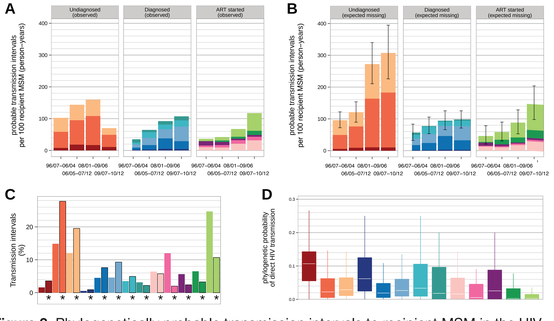


Figure 3. Phylogenetically probable transmission intervals to recipient MSM in the HIV infection and care continuum. Colour codes as in figure 1. (A) Number of observed transmission intervals. (B) Expected number of missing transmission intervals. (C) Comparison of the proportion of transmission intervals by stage between potential transmitters and phylogenetically probable transmitters (*). (D) Boxplots of phylogenetic transmission probabilities (mdian: white bar, box: interquartile range).

Table 1 Estimated proportion of transmissions to 601 recipient MSM in the Netherlands from stages in the HIV infection and care continuum

Care/treatment stage of transmitter	% of transmissions by time of diagnosis of recipient MSM (95% confidence interval)				
	Overall (n=601)	96/07-06/04 (n=153)	06/05-07/12 (n=143)	08/01-09/06 (n=149)	09/07-10/12 (n=156)
Undiagnosed (total)	69.2 (66.3-72.4)	68.4 (61.9-74.5)	70.5 (64.7-76.4)	69.7 (64.5-75.4)	68.3 (63.7-73.9)
- Recent infection at diagnosis	17.8 (15.7-22.4)	13 (8.6-22.2)	23.4 (17.2-32.4)	18.6 (12.9-25.6)	16.6 (12.3-22.7)
- Chronic infection at diagnosis	27.3 (24.8-30.1)	26.7 (21.2-33.3)	27.6 (22-33.2)	28.4 (23.7-33.8)	26.8 (22.4-31.3)
- Unknown if recent	24.1 (20.6-26)	28.8 (20.8-33.1)	19.6 (13.8-24.2)	22.7 (17.5-27.7)	24.8 (19.5-30.3)
Recently Infected (among undiagnosed)	>39.4 (35.5-46.2)	>32.8 (22.4-48.2)	>45.9 (36.3-57.4)	>39.5 (29.8-49.7)	>38.3 (30.2-48.5)
Diagnosed (total)	23.7 (21-25.9)	23.4 (18.4-28.5)	24.2 (19.1-29.2)	23.9 (18.7-28.7)	23.3 (19-27.1)
- Diagnosed < 3mo, Recent infection at diagnosis	2.6 (2-3.3)	1.7 (0.8-3.5)	2.7 (1.4-4.6)	2.1 (1.3-3.4)	3.6 (2.4-4.8)
- CD4 progression to >500	9.2 (7.3-10.5)	9.7 (6.2-13.3)	8.3 (4.9-11.3)	10.8 (7.3-13.9)	8 (5.4-9.8)
- CD4 progression to [350-500]	5.9 (4.9-7.2)	3.7 (2.1-6.5)	6.9 (4.6-9.8)	4.9 (3.4-7.3)	8 (5.7-10.4)
- CD4 progression to <350	3.1 (2.3-3.9)	2.3 (1-4)	4.4 (2.5-6.7)	3.7 (1.9-5.6)	2.2 (1.4-3.2)
- No CD4 measured	2.9 (2.2-3.8)	5.9 (3.4-8.2)	1.9 (0.9-3.2)	2.3 (1-3.8)	1.4 (1-2.4)
ART initiated (total)	7.1 (5.9-8.6)	8.1 (5.2-12.1)	5.2 (3.3-7.9)	6.4 (4.2-9.1)	8.5 (6-11.2)
- Before first viral suppression	2.3 (1.9-3.2)	2.3 (1-4.3)	1.2 (0.5-2.6)	2 (1.2-3.1)	3.8 (2.5-5.6)
- After first viral suppression, No viral load measured	1 (0.4-1.3)	1.6 (0.2-3)	0.7 (0.1-1.2)	0.6 (0.1-1)	1.2 (0.3-1.9)
- After first viral suppression, No viral suppression	1.5 (1-2.3)	3.1 (1.5-6.1)	1.4 (0.4-2.9)	1 (0.2-2.2)	0.5 (0.1-0.9)
- After first viral suppression, Viral suppression, 1 observation	0.6 (0.3-0.9)	0 (0-0.1)	0.5 (0.1-1.2)	0.9 (0.2-1.9)	1 (0.3-1.5)
- After first viral suppression, Viral suppression, >1 observations	1.6 (1.1-2.6)	1 (0.1-2.6)	1.4 (0.5-3)	2 (0.9-3.9)	2 (1.2-4.1)

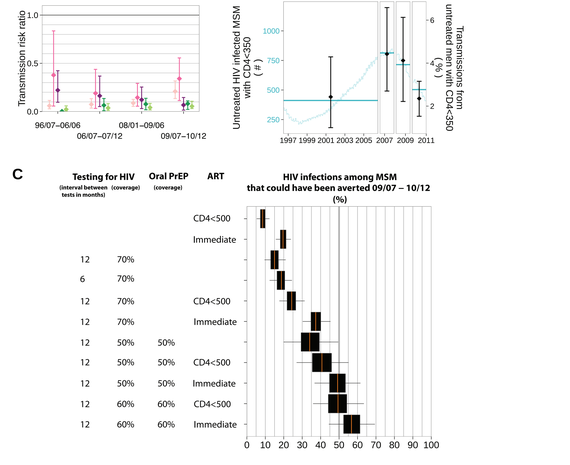


Figure 4. Impact of prevention interventions amongst MSM in the Netherlands.