REVIEW

Ending the epidemic: Critical role of primary HIV infection

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ABSTRACT

Early identification and immediate treatment of individuals newly infected with HIV is important for two reasons: it benefits the long-term health of the infected patient, and it reduces onward HIV transmission. Primary HIV infection (PHI) reflects the period following HIV acquisition during which viraemia bursts until the establishment of a stable plasma HIV-RNA level approximately six months post infection. During this period, patients are particularly contagious and are often unaware of the infection. As a consequence, PHI disproportionally affects onward transmission. During PHI the immune system is irreparably damaged and persistent viral reservoirs are formed. Initiating antiretroviral therapy (ART) during PHI could potentially lead to a functional cure through early and prolonged viral suppression. Unfortunately, symptoms of PHI are nonspecific and the diagnosis is frequently missed. This impedes timely diagnosis and prompt initiation of ART. To increase awareness and underscore the importance of immediate ART initiation, we describe here the pathogenesis, clinical presentation, and impact of treating PHI.

KEYWORDS

Acute retroviral syndrome, functional cure, HIV reservoir, HIV transmission, post-treatment control, primary HIV

INTRODUCTION

Human immunodeficiency virus-1 (HIV) acquisition often elicits a severe inflammatory response and leads to irreparable damage to the immune system. The initial phase that follows HIV infection is known as primary HIV infection (PHI) and can be defined as the interval from the detection of the virus (HIV-RNA) in the plasma until the establishment of a stable plasma HIV-RNA level (viral set point) in the presence of evolving anti-HIV antibody reactivity.[1] Initiating antiretroviral therapy (ART) during the acute phase of HIV infection reduces the inflammatory response, lowers the viral set point[2,3] and can lead to a more rapid and robust immunological recovery compared with a later start. Early in the infection, a viral reservoir of memory CD4+ T cells with viral DNA integrated into the host DNA is formed. Viral transcription in these cells is nearly absent, which hinders immunological recognition and elimination. Starting ART immediately during the early phase of infection can reduce the size of this reservoir.[4-6] Moreover, since patients are most contagious during PHI due to high viraemia,[7,8] prompt treatment initiation reduces viraemia and thereby interrupts onward transmission. For these reasons, immediate initiation of treatment upon a positive HIV test is now recommended by the current international guidelines.[1] Unfortunately, PHI remains a diagnosis that is frequently missed and patients are often unaware of having PHI at a time when they are particularly infectious. Awareness among at-risk patients as well as clinicians of the possibility of PHI is therefore of vital importance. Here we describe the pathogenesis, clinical presentation, and impact of treatment of PHI on individual and public health.

PATHOGENESIS OF PHI

To this day, the viral reservoir remains one of the major barriers to curing HIV. After entering the body, HIV reaches the draining lymph nodes where it rapidly replicates in CD4+ T cells and subsequently spreads

throughout the body.[9] Already during this phase, HIV integrates in the genome of long-lived CD4+ T cells forming a stable latently infected reservoir.[10] CD4+ T cells in the gut-associated lymphoid tissue are particularly affected and their rapid depletion results in chronic damage to the gut mucosa.[10,11] HIV replicates in the lymphoid tissues and plasma viraemia increases exponentially while the adaptive immune system is still mounting a response. This ramp-up viraemia coincides with a large burst of pro-inflammatory cytokines produced by innate immune cells, including natural killer (NK) cells. NK cells help control viral replication through recognition of infected cells via specific types of receptors.[12] Although generally the NK cell response against HIV is insufficient, marked differences in anti-HIV effects can be appreciated based on their maturation status.[13] The NK cell compartment in any individual consists of more or less matured populations, resulting in a unique profile. A more mature NK profile improves several virological and immunological markers in patients with PHI. These patients have lower viral load set points and show a better early virological response to ART initiated during PHI.[14] During the adaptive immune response, B cells produce antibodies and CD8+ T cells mount a

HIV-specific cytotoxic T cell (CTL) response. CD4+ helper T cells regulate the CTL response, but are also infected by HIV. As a consequence, they are killed by CTL or prone to virus-induced pyroptosis.[15] These combined effects result in a steep initial drop in CD4+ T cells during the first stages of PHI. This is only partly reversed through limited control over viraemia in later stages. Despite its magnitude, the immune response during PHI is unable to clear these reservoir cells. Interventions during PHI before a long-lived reservoir is established present an opportunity to achieve sustained control over the virus, and may even lead to a cure.

CLASSIFICATION OF THE STAGES OF PHI

Figure 1 provides an overview of the consecutive clinical stages following initial HIV transmission. The stages as classified by Fiebig are defined by a stepwise detectability of HIV antigens and HIV-specific antibodies using different diagnostic assays.[10,16] Successful HIV transmission marks the start of the eclipse phase. During this phase, the infection is established but viral markers in the blood are not yet detectable by routine diagnostics. At the end of the

Figure 1. *Overview of the different stages following HIV infection. The time between infection and the first detection of HIV-RNA (viral load) in plasma is referred to as the eclipse phase. Plasma HIV-RNA levels increase exponentially and peak around day 21-28. Patients can be categorised into Fiebig stages I-VI based on the sequential appearance in plasma of HIV-RNA, HIV-p24 antigen and HIV antibodies as detected by enzyme-linked immunosorbent assay (ELISA), and antibodies directed against several structural viral proteins, including p31 as detected by Western blot. Progression to Fiebig VI marks the onset of the early chronic stage during which the plasma HIV-RNA stabilises and a viral set point is established. A plus sign indicates the presence, a minus the absence of a marker, and a plus-minus sign a borderline-positive result. Adapted from McMichael et al.[10] and Cohen et al.[56]*
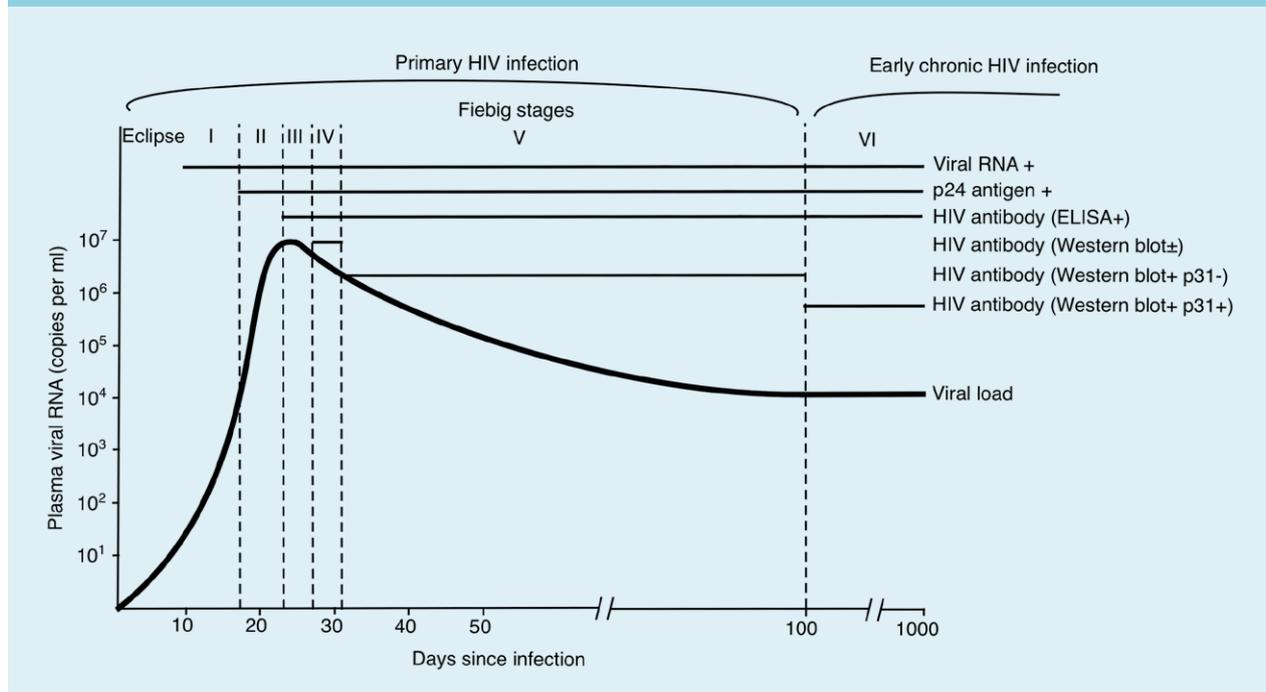
eclipse phase, the emergence of plasma HIV-RNA above the level of detection (approximately 11 days post infection) marks the start of Fiebig stage I. The detection of p24 antigen one week later marks Fiebig stage II. The plasma HIV-RNA increases exponentially and peaks between day 21 and 28 post infection, after which a slower decrease in plasma viral RNA follows. Fiebig stages III to V are based on the sequential detection of HIV-specific antibodies by enzyme-linked immunosorbent assay (ELISA) or Western blot. Progression to Fiebig VI marks the onset of the early chronic stage during which the plasma HIV-RNA stabilises and a viral set point is established.

CLINICAL PRESENTATION

Around two weeks after HIV acquisition, patients commonly experience symptoms that suggest a mononucleosis-like illness known as acute retroviral syndrome.[17-21] The acute illness may last from a few days to more than 10 weeks, but generally the duration is less than 14 days.[22,23] The estimated proportion of patients who seek professional medical care for their PHI-associated symptoms ranges from 53% to 87%.[17,20,24,25] One study estimated the prevalence of PHI among patients seeking care for fever or rash to be 0.5-0.7%.[26] Unfortunately, when patients present at healthcare facilities, PHI is hard to recognise due to the brevity of the symptomatic phase and nonspecific symptoms. In addition, in spite of current guidelines recommending pro-active testing,[27] the frequency of routine HIV testing of high-risk individuals by both primary and secondary care clinicians is low.[28-30] In Kenya, Sanders and colleagues identified seven characteristics that are independent risk factors of PHI: a younger age (18-29 years), fever, fatigue, body pains, diarrhoea, sore throat, and genital ulcer disease.[31] Based on those findings, they proposed and tested a targeted risk score algorithm to detect PHI.[31,32] In the Netherlands, a similar PHI testing strategy was developed as part of the H-team, an initiative originally launched by the late Professor Joep Lange.[33] This strategy includes a risk score algorithm aimed at men who have sex with men and involves standard of care HIV testing as well as a novel point of care (POC) RNA rapid test at the Amsterdam Public Health Service. Of 206 eligible men who presented for testing between August 2015 and January 2017, 17 men were newly diagnosed with HIV, 2 of whom were diagnosed as Fiebig I (RNA POC positive, p24 negative, antibody negative), 8 as Fiebig II (RNA POC positive, p24 positive, antibody negative), and 7 as Fiebig III-V (RNA POC positive, p24 positive and antibody positive).[34] Although these findings show that effective screening strategies can lead to diagnosis of patients in the early Fiebig stages, various studies in both resource-rich and low-resource settings indicate that regardless of clinical criteria, identification of PHI remains difficult.[19,21,22] *Table 1* presents a list of commonly considered differential diagnoses mimicking PHI in potential risk groups, including diagnostic tests that can help to differentiate. Given the wide range of symptoms associated with PHI, clinicians should have a low threshold to consider HIV testing. Moreover, awareness among clinicians of PHI in high-risk groups such as men who have sex with men, heterosexual individuals with multiple sexual partners, and migrants from areas with a high HIV prevalence is critical. When such high-risk patients present with signs and symptoms of syphilis, other STDs, or mononucleosis-like symptoms, clinicians must consider PHI as a possible co-infection or even the main cause of the clinical presentation. Finally, when known high-risk patients present with new symptoms associated with PHI clinicians should repeat HIV testing even if a very recent negative HIV test is available, because the diagnostic window of PHI is so narrow.[35]

IMPACT ON PUBLIC HEALTH

In 2011, Cohen and colleagues highlighted the potential impact of treatment of HIV on public health by showing that initiating ART immediately after diagnosis almost eliminated the risk of HIV transmission to an uninfected person in heterosexual serodiscordant couples.[36] Since PHI accounts for approximately half of onward HIV transmission in resource-rich settings,[37] treatment of PHI presents an effective tool to prevent onward transmission. Indeed, modelling studies indicate that early detection of PHI and an immediate start of ART provide an important opportunity for prevention of transmission, potentially even for HIV elimination.[38-40] Obviously, early ART initiation should not preclude patient support and risk reduction counselling, or other modifications of sexual risk behaviours.[41] In the Netherlands, general practitioners, community health services and STI clinics diagnose the majority of HIV infections (approximately 60%).[42] Unfortunately, observational studies found that PHI represents only 3.4% of all new HIV diagnoses.[43] Even in low prevalence areas where repeated HIV testing will predominantly yield negative test results, identification of only a few additional cases of PHI due to increased screening and pro-active testing of high-risk populations is modelled to be cost-effective.[44,45] Failure to identify PHI may compromise HIV prevention efforts and hinder the potential population-wide benefits. Therefore, continuous pro-active HIV testing of high-risk patients by healthcare professionals from all disciplines, and expanding coverage by including strategies such as HIV self-testing, are needed.[46]

Table 1. *Common differential diagnoses, possible differentiating diagnostics, and risk factors in patients presenting to the internal medicine department with PHI-associated symptoms*

Signs and symptoms[19,21,31]	Differential diagnosis and differentiating diagnostic assays	Sociodemographic and behavioural factors[27,31]
Reported symptoms:	Recent EBV infection	HIV endemic area[3,4]
Fever[1]	- Serology: EBV VCA-IgM, EBV VCA-IgG, EBV NA-IgG, EBV EA-IgG; PCR	
Headache[1]		STI endemic area[3,5]
Diarrhoea[1]	Recent CMV infection	
Fatigue[1]	- Serology: CMV IgM and IgG, CMV IgG avidity; PCR	MSM
Body ache (arthralgia, myalgia)[1]	Influenza infection	Prostitutes and their visitors
Swollen lymph nodes[1]	- Culture or PCR on throat swab, or bronchial wash, nasal or endotracheal aspirate, sputum	
Night sweats[1]		
Rash[1]		IV drug users
Weight loss[1]	Acute viral hepatitis A/B/C/E	
Sore throat	- Serology: HAV IgM/IgG, HBV (HBsAg, anti-HBc), HCV IgG, HEV IgG; liver function tests; PCR HAV-RNA, HBV-DNA, HCV-RNA, HEV-RNA	(Ex) prisoners
Coughing		
Malaise		Those with a sexual partner from the above groups
Nausea	TBC infection[2]	
Vomiting	- Auramine stain, culture or PCR on sputum, urine, lymph nodes, pleural effusion, or CSF	
Loss of appetite		
Genital lesions or discharge	Primary or secondary syphilis[2]	Age (18-29 years)
	- Non-treponemal test (VDRL or RPR); treponemal test (TPHA/TPPA, FTA-ABS); dark field microscopy, PCR on syphilitic lesions	>1 sex partner in the past 2 months
Physical exam signs:		
Rash[1]	Chlamydia/LGV, Gonorrhoea urethritis, pharyngitis or proctitis[2]	
Extra inguinal lymphadenopathy >2 sites[1]	- Gram stain; PCR on swab from rectum, anus, vagina, ulcer, oropharynx or conjunctiva, or on urine	
Pharyngitis[1]	Other (suspected SLE, ITP, IBD, gastro enteritis, meningitis/encephalitis, primary immunodeficiencies, travel-related pathogens)	
Oral ulcers[1]		
Genital ulcers[1]	- Depending on the specific differential, for example ANA, anti-dsDNA, biopsy; complete blood count, peripheral blood smear, DAT; colonoscopy, biopsy, stool culture, triple faecal test, immunoglobulins	
Oral thrush		
Genital warts		
Vaginal candidiasis		
Proctitis		

[1]Commonly reported signs and symptoms[21]
[2]In case of TBC, or syphilis, chlamydia, gonorrhoea, or any other STI, always consider HIV as a possible co-infection
[3]First and second generation immigrants
[4]HIV endemic area: Sub Sahara Africa, Caribbean[57]
[5]STI endemic area: Surinam, former Netherlands Antilles, Turkey, Morocco, Africa, South America, Asia, Eastern Europe[58]
EBV = Epstein-Barr virus, IgM = immunoglobulin M, VCA = viral capsid antigen, IgG = Immunoglobulin G, NA = nuclear antigen, PCR = polymerase chain reaction, CMV = cytomegalovirus, HCV = hepatitis C virus, HBV = hepatitis B virus, HBsAg = hepatitis B surface antigen, anti-HBc = anti-hepatitis B core antigen, HAV = hepatitis A virus, HEV = hepatitis E virus, TBC = tuberculosis, CSF = cerebrospinal fluid, VDRL = venereal disease research laboratory, RPR = rapid plasma reagin, TPHA = treponema pallidum hemagglutination assay, TPPA = treponema pallidum particle agglutination assay, FTA-ABS = fluorescent treponemal antibody absorbed, LGV = lymphogranuloma venereum, SLE = systemic lupus erythematosus, ITP = idiopathic thrombocytopenic purpura, IBD = inflammatory bowel disease, ANA = antinuclear antibody, anti-dsDNA = anti-double stranded DNA, DAT = direct antiglobulin Test, HIV = human immunodeficiency virus, STI = sexually transmitted infection, MSM = men who have sex with men, IV = intravenous

IMPACT ON INDIVIDUAL HEALTH

The best practice for clinical management of PHI is a subject of ongoing research. Ananworanich and colleagues found that T cell depletion and HIV reservoir seeding begins in the earliest days after HIV infection, and that commencing ART during this crucial period limits CD4+ T cell destruction and the HIV reservoir size.[47] These findings suggest a promising scenario where intervention with ART during PHI leads to favourable long-term viral and immunological outcomes compared with a deferred start of therapy. In recent years, three prospective, randomised controlled multicentre studies have shown individual health benefits of ART initiated during PHI.[2,3,48] The Short Pulse Anti-Retroviral Therapy at Seroconversion (SPARTAC) trial is the largest multicentre randomised controlled trial to date involving 366 PHI patients.[3] In this study, a 48-week course of ART during PHI resulted in significant CD4+ T cell improvement and a lower plasma viral set point after treatment interruption. The Dutch Primo-SHM trial involving 115 PHI patients showed a similar trend.[2] The Setpoint study (ACTG-A5217) included 130 PHI patients and was in fact prematurely terminated due to better outcomes in the group receiving immediate treatment.[48] Importantly, although these studies indicate that starting and then stopping treatment is a beneficial and potential therapeutic strategy, a large, long-term randomised controlled trial of patients with chronic HIV infection found treatment interruption to have harmful effects,[49] and consequently current guidelines recommend uninterrupted treatment.[1] Moreover, precisely which combination of antiretroviral medication presents the optimal treatment of PHI, and whether intensification of ART can yield greater benefits in reducing markers for HIV reservoir size and immune activation, is presently unclear. A small randomised controlled trial by Ananworanich et al. in which drugs that can block viral cellular entry (maraviroc), and integration (raltegravir) were added to a standard regimen with nucleoside reverse-transcriptase inhibitors (tenofovir and emtricitabine) and a non-nucleoside reverse-transcriptase inhibitor (efavirenz) did not show an additional effect in reducing the viral burden and HIV reservoir seeding in Thai individuals.[50] Furthermore, while early intervention seems favourable, data on definite clinical endpoints such as mortality are still unavailable. Nonetheless, these findings support the rationale of ART initiation during PHI at the earliest stage possible, before the immune system suffers irreparable damage and the reservoir size is established.

POTENTIAL FOR CURE

Initiating ART during PHI offers the potential for what is known as a functional cure. A patient is considered functionally cured, or a post-treatment controller, when ART can be interrupted without subsequent rebound plasma viraemia or progressive loss of cellular immunity. The potential for achieving a functional cure when treatment is started during PHI is reflected by a number of studies. The case of the Mississippi infant is illustrative. Since the baby was born to an HIV-infected mother who had received no prenatal care, it began receiving full ART 30 hours after birth. ART was interrupted and the baby was withdrawn from care by the mother after 18 months of continuous ART, but surprisingly, this infant sustained an undetectable plasma viral load at the age of three years when re-entering medical care.[51] Unfortunately, two months before reaching the age of 4 years viral rebound occurred and the girl had to be started on ART again. Similar observations were derived from the RV254/SEARCH 010 study, an ongoing prospective, longitudinal cohort of PHI patients in Thailand that was initiated in 2009. The authors of this study were the first to imply immediate treatment of PHI as a promising strategy to reduce reservoir formation to eventually achieve sustained drug-free viral remission.[47] A landmark study on post-treatment controllers is the Viro-Immunological Sustained CONtrol after Treatment Interruption (VISCONTI) cohort.[5] In this study, 14 post-treatment controllers were identified out of a much larger cohort of PHI patients who started ART during PHI and who subsequently interrupted ART after a median of three years. These 14 patients remained aviraemic for several years after ART interruption.[5] The small viral reservoir and altered CD4+ T cell subsets in these individuals have been hypothesised to be contributing factors. In line with this assumption, post-treatment controllers are far less frequently observed when ART is started in the chronic stage of HIV infection. Other treatment interruption studies have identified similar patients.[52] Furthermore, longer exposure to ART is associated with a greater chance of post-treatment control in patients with PHI,[53] and previous evidence points towards uninterrupted treatment.[49] Therefore, stopping ART in the context of a cure study should be carefully planned, HIV-RNA guided, and closely monitored. Unfortunately, clear markers to predict sustained virus control after treatment of PHI have yet to be elucidated. Clearly, post-treatment controllers hold an important clue with regard to future curative efforts, but for the majority of individuals including those with PHI, treatment interruption results in viral rebound and continuous ART remains a necessity.

CURRENT AND FUTURE PROSPECTS

In line with current guidelines, patients should be informed about the benefit of starting ART following

PHI diagnosis, and be counselled about the high risk of transmission as long as they are highly viraemic, preventive measures, and the importance of notifying partners.[1] The European AIDS Clinical Society (EACS) advises that clinicians should be familiar with local routes to ensure instant referral to an HIV specialised centre to start treatment as soon as possible, and preferably combine this with enrolment into clinical studies investigating HIV curative strategies.[1] Such a study is the Netherlands Cohort Study on Acute HIV Infection (NOVA), part of the H-Team initiative, which intends to promote prompt linkage to care and immediate ART initiation in all PHI patients in the Netherlands. Such initiatives also offer opportunities for a detailed characterisation of the viral reservoir and could provide further insights into the early immune response to HIV. By obtaining a better understanding of the factors related to functional cure, such studies can help optimise treatment strategies and assist in identifying patients who could benefit most from future strategies to achieve post-treatment control, including cure strategies with therapeutic vaccination or specific agents targeting the HIV reservoir. While work on a future cure is in progress, other initiatives to halt onward HIV transmission are needed. For example, pre-exposure prophylaxis has been shown to be highly effective[54,55] and thereby would present an important strategy to reduce the incidence of HIV infection and can aid in HIV elimination.

CONCLUSION

Greater clinical awareness of PHI among clinicians from all disciplines, pro-active and repeated HIV testing, and fast linkage to care in order to facilitate an immediate start of ART merit our attention. First, it helps to prevent onward transmission and could ultimately lead to HIV elimination. Second, it improves an individual patient's health by limiting both reservoir size and immune damage. This could aid future efforts to achieve a functional cure. Ongoing studies involving patients with PHI remain a necessity, however. Thirty-five years on, more than 40 million people have died due to HIV globally. In the Netherlands, approximately 900 people still become infected with HIV every year. PHI remains a clinical and public health emergency that requires early diagnosis and immediate intervention. If we are to finally end the HIV epidemic, PHI should be on the agenda.

DISCLOSURES

All authors declare that they have no conflict of interest. No financial support was received for the conduct of this study or preparation of this manuscript.

REFERENCES

1. European AIDS Clinical Society (EACS) Guideline Version 8.2 (2017) page 10. Accessed on July 8, 2017. [Available from: http://www.eacsociety.org/files/guidelines_8.2-english.pdf.

2. Grijsen ML, Steingrover R, Wit FW, et al. No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: the randomized Primo-SHM trial. PLoS Med. 2012;9:e1001196.

3. Idler S, Porter K, Ewings F, et al. Short-course antiretroviral therapy in primary HIV infection. N Engl J Med. 2013;368:207-17.

4. Ananworanich J, Sacdalan CP, Pinyakorn S, et al. Virological and immunological characteristics of HIV-infected individuals at the earliest stage of infection. J Virus Erad. 2016;2:43-8.

5. Saez-Cirion A, Bacchus C, Hocqueloux L, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog. 2013;9:e1003211.

6. Strain MC, Little SJ, Daar ES, et al. Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. J Infect Dis. 2005;191:1410-8.

7. Pilcher CD, Joaki G, Hoffman IF, et al. Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. AIDS (London, England). 2007;21:1723-30.

8. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis. 2005;191:1403-9.

9. Whitney JB, Hill AL, Sanisetty S, et al. Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys. Nature. 2014;512:74-7.

10. McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF. The immune response during acute HIV-1 infection: clues for vaccine development. Nat Rev Immunol. 2010;10:11-23.

11. Veazey RS, DeMaria M, Chalifoux LV, et al. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. Science. 1998;280:427-31.

12. Alter G, Rihn S, Walter K, et al. HLA class I subtype-dependent expansion of KIR3DS1+ and KIR3DL1+ NK cells during acute human immunodeficiency virus type 1 infection. J Virol. 2009;83:6798-805.

13. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol. 2001;22:633-40.

14. Gondois-Rey F, Cheret A, Mallet F, et al. A Mature NK Profile at the Time of HIV Primary Infection Is Associated with an Early Response to cART. Front Immunol. 2017;8:54.

15. Doitsh G, Galloway NL, Geng X, et al. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. Nature. 2014;505:509-14.

16. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS (London, England). 2003;17:1871-9.

17. Tindall B, Barker S, Donovan B, et al. Characterization of the acute clinical illness associated with human immunodeficiency virus infection. Arch Intern Med. 1988;148:945-9.

18. Richey LE, Halperin J. Acute human immunodeficiency virus infection. Am J Med Sci. 2013;345:136-42.

19. Robb ML, Eller LA, Kibuuka H, et al. Prospective Study of Acute HIV-1 Infection in Adults in East Africa and Thailand. N Engl J Med. 2016;374:2120-30.

20. Sanders EJ, Wahome E, Mwangome M, et al. Most adults seek urgent healthcare when acquiring HIV-1 and are frequently treated for malaria in coastal Kenya. AIDS (London, England). 2011;25:1219-24.

21. Wood E, Kerr T, Rowell G, et al. Does this adult patient have early HIV infection?: The Rational Clinical Examination systematic review. JAMA. 2014;312:278-85.

22. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med. 1996;125:257-64.

23. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. N Engl J Med. 1998;339:33-9.

24. Hightow-Weidman LB, Golin CE, Green K, Shaw EN, MacDonald PD, Leone PA. Identifying people with acute HIV infection: demographic

features, risk factors, and use of health care among individuals with AHI in North Carolina. AIDS Behav. 2009;13:1075-83.

25. Sudarshi D, Pao D, Murphy G, Parry J, Dean G, Fisher M. Missed opportunities for diagnosing primary HIV infection. Sex Transm Infect. 2008;84:14-6.

26. Coco A, Kleinhans E. Prevalence of primary HIV infection in symptomatic ambulatory patients. Ann Fam Med. 2005;3:400-4.

27. Van Bergen JEAM, Dekker JH, Boeke AJP, et al. Nederlands Huisartsen Genootschap (NHG) Standaard – Het soa-consult. Huisarts Wet 2013;56:450-63.

28. Daar ES, Pilcher CD, Hecht FM. Clinical presentation and diagnosis of primary HIV-1 infection. Curr Opin HIV AIDS. 2008;3:10-5.

29. Yerly S, Hirschel B. Diagnosing acute HIV infection. Expert Rev Anti Infect Ther. 2012;10:31-41.

30. Joore IK, Bom BCJ, Van Sighem AI, Geerlings SE, Prins JM, Van Bergen JEAM. Proactiever testen op hiv is nodig. Huisarts Wet. 2017;60:24-6.

31. Sanders EJ, Wahome E, Powers KA, et al. Targeted screening of at-risk adults for acute HIV-1 infection in sub-Saharan Africa. AIDS (London, England). 2015;29 Suppl 3:S221-30.

32. Sanders EJ, Mugo P, Prins HA, et al. Acute HIV-1 infection is as common as malaria in young febrile adults seeking care in coastal Kenya. AIDS (London, England). 2014;28:1357-63.

33. HIV Tranmission Elimination AMsterdam initiative (H-TEAM). Date accessed July 8, 2017. Available at http://hteam.nl/en/about/

34. Dijkstra M, Hoornenborg E, Davidovich U, et al. Implementation of a rapid diagnostic and referral strategy to identify acute HIV-1 infections in Amsterdam Conference on Retroviruses and Opportunistic Infections (CROI); Date accessed July 8, 2017. Available at http://www.croiconference.org/sites/default/files/posters-2017/887_Dijkstra.pdf; Boston, Massachusetts, USA2017.

35. Feinberg J, Keeshin S. Management of Newly Diagnosed HIV Infection. Ann Intern Med. 2017;167:ITC1-ITC16.

36. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365:493-505.

37. Brenner BG, Roger M, Routy JP, et al. High rates of forward transmission events after acute/early HIV-1 infection. J Infect Dis. 2007;195:951-9.

38. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373:48-57.

39. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet. 2010;376:532-9.

40. Powers KA, Ghani AC, Miller WC, et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. Lancet. 2011;378:256-68.

41. Van Griensven F, Phanuphak N, Kroon EDMB, et al. Acute HIV infection detection and control reduces HIV infectiousness and transmission risk behavior among men who have sex with men in Bangkok, Thailand. IAS 2013: 7th IAS conference on HIV pathogenesis, treatment and prevention; Kuala Lumpur, Malaysia 2013.

42. Van Sighem A, Boender S, Wit F, Smit S, Matser A, Reiss P. Stichting HIV Monitoring (SHM). HIV Monitoring Report 2016, page 4-5. Date accessed April 17, 2017. Available at SHM_samenvatting__aanbevelingen_2016.pdf.

43. Kuruc JD, Cope AB, Sampson LA, et al. Ten Years of Screening and Testing for Acute HIV Infection in North Carolina. J Acquir Immune Defic Syndr. 2016;71:111-9.

44. Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. N Engl J Med. 2005;352:570-85.

45. Phillips AN, Cambiano V, Miners A, et al. Potential impact on HIV incidence of higher HIV testing rates and earlier antiretroviral therapy initiation in MSM. AIDS (London, England). 2015;29:1855-62.

46. Fidler S, Fox J. Primary HIV infection: a medical and public health emergency requiring rapid specialist management. Clin Med (Lond). 2016;16:180-3.

47. Ananworanich J, Schuetz A, Vandergeeten C, et al. Impact of multi-targeted antiretroviral treatment on gut T cell depletion and HIV reservoir seeding during acute HIV infection. PloS One. 2012;7:e33948.

48. Hogan CM, Degruttola V, Sun X, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. J Infect Dis. 2012;205:87-96.

49. Strategies for Management of Antiretroviral Therapy Study G, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355:2283-96.

50. Ananworanich J, Chomont N, Fletcher JL, et al. Markers of HIV reservoir size and immune activation after treatment in acute HIV infection with and without raltegravir and maraviroc intensification. J Virus Erad. 2015;1:116-22.

51. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med. 2013;369:1828-35.

52. Li JZ, Etemad B, Ahmed H, et al. The size of the expressed HIV reservoir predicts timing of viral rebound after treatment interruption. AIDS (London, England). 2016;30:343-53.

53. Fidler S, Olson AD, Bucher HC, et al. Virological Blips and Predictors of Post Treatment Viral Control After Stopping ART Started in Primary HIV Infection. J Acquir Immune Defic Syndr. 2017;74:126-33.

54. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016;387:53-60.

55. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015;373:2237-46.

56. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. N Engl J Med. 2011;364:1943-54.

57. UNAIDS AIDSinfo. Number of people living with HIV (2015). Date accessed June 7, 2017. Available at http://aidsinfo.unaids.org/ [Internet].

58. Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Lijst soa/hiv-endemische landen (2015). Date accessed June 7, 2017. Available at www.rivm.nl Landenlijst_endemisch_6-1-2015(1).xls [Internet].

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