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Primary HIV infection: a medical and public health emergency requiring rapid specialist management

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ABSTRACT

Primary HIV infection (PHI) refers to the first six months following HIV acquisition and represents a unique opportunity for expedited diagnosis, and consideration of rapid antiretroviral therapy (ART) initiation to improve immune function, reduce the size of the viral reservoir and limit the risk of onward viral transmission. Failure to diagnose and rapidly treat individuals with PHI has significant individual and public health implications. The Strategic Timing of AntiRetroviral Treatment trial recently identified a clinical benefit of immediate ART over deferral of treatment according to CD4 count threshold, and has led to rapid changes in World Health Organization and specialist national guidelines. For all individuals living with HIV, the offer of immediate therapy irrespective of CD4 count is now recommended. This paper summarises the presentation and management of PHI, incorporating current research and guideline changes and discusses the role of PHI in onward transmission.

HIV in the UK

At the end of 2014 there were an estimated 103,700 individuals living with HIV;[1] 6,151 individuals were newly diagnosed HIV positive with rates highest in men who have sex with men (MSM) (n = 3,360). Of new diagnoses, 22% had proven recent infection and this was highest among gay and bisexual men. This increase in HIV incidence has occurred despite increased HIV testing to reduce those undiagnosed and effective use of antiretroviral therapy (ART), which substantially reduces infectiousness.[2–4] The risk of onward transmission correlates with plasma viral load.[5] Individuals at the earliest stage of infection, referred to as primary HIV infection (PHI) are particularly infectious as they often have extremely high viral load levels, the transmitted virus itself has characteristics that enhance the spread of infection and concomitant sexually transmitted infection (STI) may increase HIV infectiousness.[6] The majority of HIV transmissions occur from individuals who are unaware of their diagnosis or not on suppressive ART. Therefore correct diagnosis and linkage to care and treatment are critical to reducing HIV incidence in the UK.[7]

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Diagnosis of PHI

PHI represents the initial six months following HIV acquisition. This stage of infection is associated with a high-level plasma viraemia which is subsequently limited by host immune responses which confer symptomatic and partial immunological recovery for the majority of individuals.[8] In the absence of ART a gradual decline in peripheral CD4 T cells is observed; on average between 50–70 cells/year.[9] Viral dissemination and the establishment of a viral reservoir throughout the body occurs rapidly after acquisition[9] and is the reason why ART cannot cure HIV infection.[10,11] Despite years of successful suppressive ART a latent pool of HIV-infected cells is thought to be the source of viral recrudescence on stopping therapy.[11]

Challenges of PHI diagnosis

The standard test for HIV infection is an HIV-specific antibody, which can be performed as a point-of-care finger prick test or a laboratory fourth generation combination assay detecting the presence of HIV antibody and or viral gag protein (p24).[12] Individuals presenting very soon after HIV acquisition, with acute infection, may present prior to the production of detectable levels of HIV-specific antibodies, using routine point-of-care or laboratory assays. In these situations, confirmation of an HIV diagnosis can be made from venous blood samples sent to a virology laboratory where the presence of viral proteins (p24) or viral HIV DNA or RNA can be made.[13] Laboratory third generation tests do not detect viral gag protein (p24) and therefore are less able to detect early infection prior to the development of detectable levels of HIV antibody. The lack of detectable antibodies in the initial stages of infection makes this a difficult diagnosis to make using current standard tests. The window period (ie the time between transmission and production of HIV antibodies when an HIV enzyme-linked immunosorbent assay result may be falsely negative) for a third generation antibody test is 21 days and for a fourth generation combination assay (ie the presence of p24 antigen in the absence of antibody) is 14 days after infection.[14] The recent HIV test algorithm (RITA), carried out by Public Health England, can also identify recent infection providing the clinic is part of the surveillance network.[15] Table 1 summarises the different tests available to diagnose HIV infection.

The majority of symptoms associated with PHI are non-specific[15] and hence often misdiagnosed or overlooked. Table 2 highlights some of the symptoms, signs and recommended tests that can be associated with PHI. In view of the increased

Table 1. Methods of diagnosis of PHI.

Diagnostic test	Diagnostic method	Time from infection to detection
HIV antibody test	Venous blood; POC finger prick test; oral swab test; self-testing	21 days (discordance in POC results strongly suggests PIH)
p24 antigen test	Venous blood sample fourth generation combo-antigen-antibody test	14 days
RITA	Venous blood PHE	Up to 16 weeks from estimated date of infection
HIV RNA or DNA	Venous blood PCR	7 days of infection

PHI = primary HIV infection; PCR = polymerase chain reaction; PHE = Public Health England; POC = point of care; RITA = recent HIV test algorithm.

risk of missed diagnoses of acute HIV infection, the presence of certain indicator diseases should trigger the offer of HIV testing,[16,17] for individuals presenting with signs or symptoms of Epstein–Barr virus, cytomegalovirus, secondary syphilis, tuberculosis and bacterial pneumonia. As a result of the challenges with current technology at accurately diagnosing acute HIV infection, encouraging both access and increasing the frequency of HIV testing among those at highest risk are key to improving timely identification of PHI. Increasing HIV testing outside of genitourinary medicine[18] and the recent legalisation of self testing[19] are anticipated to improve coverage.

Initial management and counselling

Heightened awareness of PHI with urgent referral for ART discussion has the potential to enhance clinical outcome and reduce the risk of onward viral transmission.

Initial counselling must be provided, as well as urgent contact tracing to enable urgent HIV testing of partners and post-exposure prophylaxis (PEP),[20] if exposure occurred within the preceding 72 hours. Rarely PHI can present with opportunistic infections or severe neurological involvement requiring urgent management, otherwise, PHI tend to be mild, temporary and self-limiting. Interventions to consider at this time include ART, screening and treatment of concomitant STI, and the promotion of immediate changes in sexual behaviour.[21] These include consistent condom use, limiting drug and alcohol intake (which may impair the ability to negotiate safe sex), and the incorporation of alternative sexual practices that do not involve the exchange of body fluids.

Keeping individuals engaged in care and not passing HIV on during this period of hyper-infectiousness is of paramount importance. Initial counselling is essential as well as rapid contact tracing to enable urgent HIV testing and provision of PEP (if exposure occurred within preceding the 72 hours) to partners.

Key points

Identification of primary HIV in any medical setting remains a priority.

Encouragement of frequent testing across all settings.

Rapid referral to an HIV specialist is essential.

There is a time window of opportunity in ART within which immediate ART initiation confers enhanced clinical benefit.

KEYWORDS: Acute HIV infection, immediate clinical HIV management, antiretroviral therapy ■

Antiretroviral treatment

The recent change in UK treatment guidelines[22] recommending initiation of ART for all people living with HIV irrespective of CD4 count is similarly pertinent to those diagnosed with PHI, and reflects new evidence from the Strategic Timing of AntiRetroviral Treatment[23] trial. The trial identified a significant reduction in the combined endpoint of AIDS events, serious non-AIDS events and death for immediate initiation of ART for all people living with HIV.

PHI differs from chronic infection as there are reasons to fast track individuals with PHI for immediate ART initiation, whereas those with asymptomatic chronic infection and CD4 counts >350 cells/cm^3 do not have the same level of urgency to start therapy.

- Preservation of CD4 T lymphocytes (total CD4 counts and ratio of CD4:8 T cells) correlates with all-cause mortality and recovery is directly related to the timing of ART initiation.[24–26]
- Reduction in the enhanced risk of onward transmission of HIV associated with PHI.[27–32]
- Limitation in the size of latent pool of HIV-infected cells; the viral reservoir, [33,35] which has been associated with

Table 2. Symptoms, signs and recommended diagnostic tests associated with PHI.

Symptoms	Signs	Test	Differential diagnosis
Fever, night sweats, general malaise	Weight loss, lymphadenopathy	FBC, LFT, HIV antigen/antibody test, hepatitis A, B and C antibody, PCR, blood film, CRP, Paul Burnell EBV, CMV, HSV	Acute infectious cause, depending on history, acute hepatitis A, B and C, CMV, EBV, tuberculosis, malaria glandular fever, lymphoma, leukaemia, malignancy
Diarrhoea	Weight loss	Stool MCS and OCP; infection screen as above; colonoscopy and biopsy if persistent	Infectious diarrhoea inflammatory bowel disease
Rash		STS, measles, rubella	Syphilis, measles, rubella, VZV *(depending on rash)

CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein–Barr virus; FBC = full blood count; HSV = herpes simplex virus; LFT = liver function test; MCS = microscopy, culture and sensitivities; OCP = ova, cysts and parasites; PCR = polymerase chain reaction; PHI = primary HIV infection; STS = syphilis serology; VZV = varicella zoster virus.

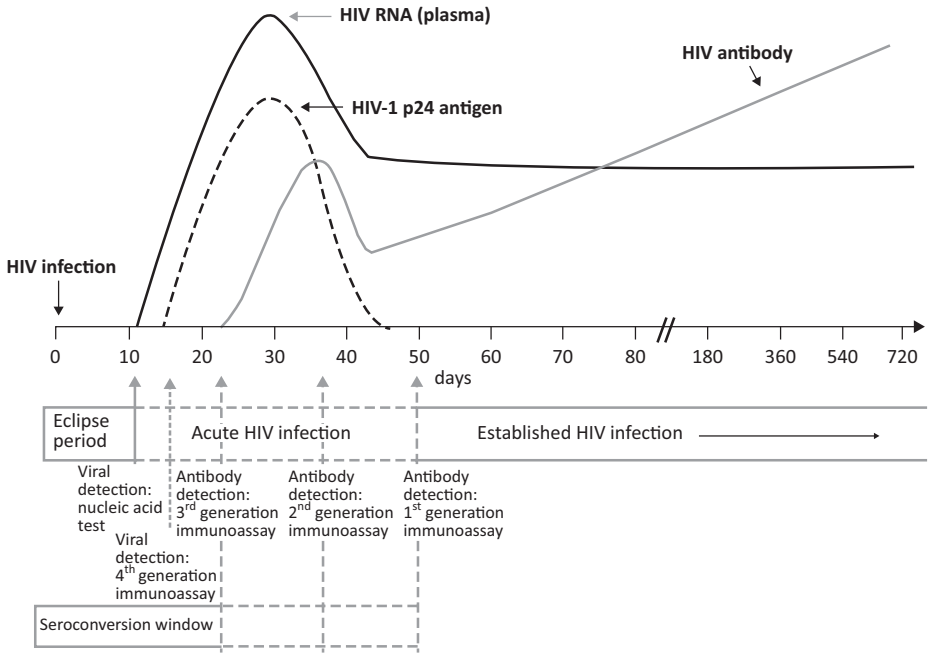

Fig 1. Tests that diagnose PHI in the absence of detectable antibody.

viral remission on stopping ARV, so called functional cure.[34,36]

- All of these benefits are observed the closer to PHI that ART is initiated, particularly in the first 12 weeks.[21,32,37,40]

Duration of ART at PHI

Three randomised controlled trials in PHI reported a modest benefit (delaying the decline in CD4 cell count, or time from PHI, to requiring lifelong ART) following a 48-week[38] or 60-week[39,40] course of ART. Interruption of therapy even if started close to the time of PHI is no longer recommended.[21] Therefore, once started, ART should be taken lifelong.

ART regimen and PHI

ART regimen should be prescribed in accordance with BHIVA guidelines[22] which is a three-drug regime; comprising a backbone of two nucleoside reverse transcriptase inhibitors and a third agent from a different class. At PHI whilst any currently approved antiretroviral combination can be commenced in PHI, preference for regimens including integrase inhibitor agents which have been shown to rapidly control viral replication should be considered especially among individuals with extremely high plasma viral load. There are no clinical, immunological or virological data supporting the initiation of more than three drug combinations. The most important factor is expedited ART initiation and good adherence. From UK observational cohort studies there is no evidence of increased rates of drug-related toxicities among individuals treated with high CD4 counts and no increased risk of development of drug resistance among individuals starting early compared with later. Viral suppression should be anticipated by 24 weeks on therapy for the majority of individuals adhering to ART. The time period between ART initiation and viral suppression remains an important risk for onward transmission and must be clearly explained.

Prevention of HIV transmission

The very high plasma viraemia, often compounded by high rates of concomitant STI and continued high-risk sexual practices among individuals who are unaware of their changed HIV status, makes the short period of PHI highly infectious. Phylogenetic studies among MSM in Brighton and other cities showed that individuals with PHI contributed over 40% of all new infections.[31,32] Indeed mathematical models suggest that PHI could be responsible for over half of all new HIV infections in focused epidemics such as the UK.[7] The use of ART in HIV-positive individuals is the most effective tool to prevent onward viral transmission among HIV serodifferent heterosexual and MSM couples. Recent PEP guidelines advise six months virological suppression before the infection transmission risk is too low to justify PEP provision.[41] At a population level, the critical barrier to prevention remains diagnosis.

Summary

Awareness of PHI among certain core high-risk groups, in particular MSM, in the UK is critical to avoid missed diagnoses which impact on individual care and the prevention of onward HIV transmission. Using increased and varied testing, and improving clinician and patient education to recognise symptoms of PHI, will improve PHI diagnosis. Prompt discussion about the benefits of initiating ART at HIV seroconversion (irrespective of CD4 count and viral load) should cover improved surrogate markers of disease progression and a marked reduction in risk of onward viral transmission. Rapid diagnosis followed by immediate risk reduction interventions, screening and treatment of concomitant STIs, and the early initiation of ART to reduce viral load are critical goals to better control the HIV epidemic.

Clinicians should be able to recognise the signs and symptoms of PHI, be confident to offer the appropriate HIV tests and be familiar with local pathways for prompt referral to specialist services. ■

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