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Use and Effectiveness of HIV Indicator Conditions in Guiding HIV Testing: A Review of the Evidence

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Authors' contributions

This work was carried out in collaboration between all authors. Author CFD designed the study, managed and performed the literature searches. Author CFD wrote the first draft of the manuscript. Authors MTM and MG helped with re-drafting and revising the article. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: To identify the most commonly reported HIV indicator conditions (HIV ICs) found in or associated with HIV infection and to review interventions incorporating HIV ICs to aid or guide offering of an HIV test and discuss their effectiveness in increasing HIV testing rates and diagnosing new cases of HIV-infection.
Methodology: The following electronic databases were searched; OVID Medline, Google, Web of Science and PubMed. We included studies conducted in high income countries within the adult population (>18yrs of age) that were published in the era of combination antiretroviral therapy between 1996 and 2016. We excluded studies relating to HIV testing or screening of pregnant women.
Results: We identified 42 studies investigating ICs associated with HIV infection either prior to or after diagnosis within primary, secondary and tertiary care settings. The most common ICs and symptoms associated with HIV infection were; sexually transmitted infections (syphilis, chlamydia, gonorrhoea and condyloma acuminata) and blood borne viruses (Hepatitis C and Hepatitis B),

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pneumonia, tuberculosis, blood dyscrasia, thrombocytopenia, oral and oesophageal candidiasis, seborrhoeic dermatitis, herpes zoster, Kaposi sarcoma, fever, weight loss, diarrhoea and lymphadenopathy. Twelve intervention studies that used HIV prediction tools and computer prompts based on HIV ICs demonstrated that these are effective in helping healthcare professionals to offer more targeted approaches to HIV testing.

Conclusion: Our review may aid policy makers and healthcare professionals in developing strategies to improve and increase HIV testing in individuals that present with defined HIV ICs. ICs have the potential to be used more effectively as triggers for earlier HIV testing and importantly for patients to receive a more timely diagnosis.

Keywords: HIV; indicator conditions; diagnosis; testing; screening; early detection; prompted; algorithm; HIV testing reminders.

1. INTRODUCTION

There are an estimated 101,200 people living with HIV in the UK of whom 13% have not yet been diagnosed and are unaware of their infection [1]. A similar percentage are found in other, socioeconomic equivalent countries [2,3]. Two thirds of new infections are likely to be transmitted from those unaware of their HIV status [4]. Treatment for HIV infection using anti-retroviral treatment (ART) is highly effective but early and prompt diagnosis of infection are paramount for greatest benefit of treatment. Recent international recommendations now state that ART should be initiated in all individuals with HIV infection irrespective of CD4 cell count [5,6]. Late diagnosis of HIV is common in Europe with 48% of HIV infected persons presenting with a CD4 cell count <350 cells/mm^3 and 28% with CD4 count < 200 cells/mm^3 in 2015 [7]. Late diagnosis is also a problem globally [8]. In England during 2015, 39% of adults newly diagnosed with HIV were diagnosed late (CD4 count < 350 mm^3) [9]. In areas of high prevalence (>2 per 1000 among 15-59-year old's), the British HIV Association (BHIVA) national guidelines recommend that all new general practice registrants and all new hospital admissions should be tested for HIV [10]. In the USA, current guidance is for routine testing among all adults that come into contact with the healthcare system [11]. Patients often present to healthcare professionals (HCPs) with symptoms or conditions that are associated with HIV called HIV indicator conditions (HIV ICs). HIV ICs are diseases and symptoms that have been associated with underlying HIV infection of which 37 HIV ICs have been documented [10]. In the primary care setting general practitioners (GP) are recommended to follow an indicator condition- guided testing approach [10,12]. All patients presenting with any HIV IC in primary care should be offered an HIV test. Research shows that often the GP or HCP are unfamiliar with HIV ICs and do not associate these conditions with HIV infection resulting in potential HIV diagnoses being missed [13,14]. There is the added complication that a high proportion of these conditions are nonspecific in nature and some symptoms resemble more mundane infections for which patients may often not seek medical advice. During the early stages of primary HIV infection (PHI) or acute retroviral syndrome (ARS) symptoms usually develop within 2 to 4 weeks after infection. Symptoms or seroconversion illness may be present in 23% to 92% of infected cases [15]. Typical symptoms include fever, fatigue, rash, nausea and headache that usually last 2 to 3 weeks and often represent the only clinical signs of HIV infection until many years later when more advanced immunosuppression may occur. Many other diverse clinical conditions may also present with these symptoms [16]. Earlier diagnosis of HIV therefore requires innovative strategies to target testing towards individuals most likely to be infected.

IC guided testing provides a valuable opportunity to identify individuals with undiagnosed HIV infection. A recent study showed that 27% of patients had presented for care at least once with HIV and/or AIDS associated conditions 3 years prior to receiving their diagnosis [17]. Because HCPs decide whether a test offer is appropriate based on the patient's symptoms and not on race, ethnicity or sexuality, IC guided testing is less stigmatising. IC guided testing also removes the need for individual risk assessment and helps to normalise testing [18]. However, there is still a compelling need to educate clinicians and GPs about HIV and incorporating IC guided testing [19] in order to decrease rates of late diagnosis. A recent review of newly infected HIV patients in Germany found that ICs were present in one fifth of late presenters [20]. Scognamiglio et al. found

that approximately 30% of newly diagnosed adults with HIV infection had reported at least one IC before HIV diagnosis and that having an HIV test within 6 months of being diagnosed with an indicator disease reduced the risk of late presentation by 50%. The HIV Indicator Diseases Across Europe Study (HIDES) [21] has raised awareness of IC based testing and developed an indicator disease testing strategy in which patients were tested routinely for HIV if presenting with preselected ICs (HIDES I & II studies) [22,23]. Data from the HIDES II audit in patients accessing care for a number of HIV ICs highlighted that testing rates in those with ICs remained low across Europe [23] with poor adherence to European guidelines recommending routine testing [21]. High HIV positivity rates were observed in individuals with AIDS defining and non-AIDS defining ICs within the HIDES study [23] and have also been reported in other studies [24]. Therefore, interventions are needed that prompt HCPs to offer a test when patients present with HIV ICs.

We review data on the most commonly reported HIV ICs found in or associated with either acute or chronic HIV infection in individuals prior to or at HIV diagnosis. In addition, we review research studies of interventions that have used HIV ICs to guide/ increase HIV testing and explore which of these interventions have been most effective in increasing HIV testing rates and case finding. Our review may aid policy makers and HCPs in developing strategies to improve and increase HIV testing in individuals that present with defined HIV ICs, and show the potential of ICs as effective triggers for HIV testing that should decrease late diagnosis.

2. MATERIALS AND METHODS

2.1 Search Strategy

We carried out a broad literature search of published documents that included peer reviewed articles in journals, reports and British HIV Association (BHIVA) conference proceedings. The following electronic databases were searched; OVID Medline, Google, Web of Science and PubMed. The search was last performed on 15th November 2016. We used a combination of focused computerised retrieval and hand searching. Hand searching involved manual page by page examination of recent BHIVA conference proceedings to identify eligible studies (abstracts from 2010 to 2017). We also manually searched reference lists of relevant articles for additional publications.

Basic searches were performed using a combination of the following keywords for ICs associated with HIV infection and interventions that had used HIV ICs to guide testing; HIV clinical indicator conditions, HIV indicator diseases, HIV symptoms, HIV test*, screen* diagnos*, HIV testing guidelines, BHIVA guidelines, HIV testing in primary care, secondary care, HIV indicator conditions and interventions, HIV testing algorithms, clinical decision support tool and HIV testing, clinical prediction tool and HIV testing, electronic reminders and HIV testing, HIV testing and electronic systems, computer system data and HIV testing, general practice data and HIV testing.

2.2 Selected Studies

Papers included in the review had to meet the following inclusion criteria: studies conducted in high income countries that had investigated associations of ICs with HIV infection among adult populations (>18 years of age) and interventions that had used ICs to guide HIV testing published in the combination ART era (1996-2016). Documents had to be accessible through the University of Bristol institutional library service. We excluded studies relating to HIV testing or screening of pregnant women and HIV infection in children.

3. RESULTS

3.1 Associations of HIV Indicator Conditions (HIV ICs) with HIV Infection

3.1.1 Characteristics of studies

The review found 42 studies which investigated associations of ICs with testing positive for HIV infection (Table 1). Of these, 37 studied individuals prior to or after diagnosis, and 5 only studied signs and symptoms in individuals specifically diagnosed with acute HIV infection (AHI)/primary HIV infection (PHI).

Studies included in this analysis were: peer reviewed papers (n= 35) abstracts from BHIVA conference proceedings (n= 7). Locations of included studies were: UK and Northern Ireland (n=14), France (n= 1), Italy (n= 1), Germany (n=

1), Spain (n=4), Sweden (n=1), Switzerland (n=1), Amsterdam (n=1), Denmark (n=2), Europe wide (n=4), Japan (n=1), Canada (n=1), USA (n= 7), Brazil (n=1), Worldwide (n = 2). Studies used a variety of different data collection methods including: cross sectional analysis (n= 4), prospective analysis (n= 6), retrospective analysis (n=19), retrospective/audit (n = 4), case note review (n=2), case/control studies (n=3), service evaluation (n=1), observational study (n=1) and information gathered from review articles (n= 2). Studies were carried out in the following settings: primary care (n= 8), secondary care (n= 17), both primary and secondary care settings (n=1), sexual health clinic & secondary care (n= 2), sexual health clinics (n=5), HIV and medical centres (n= 6), public health surveillance database (n= 1), collection of different settings (e.g reviews) (n= 2).

3.1.2 Most commonly reported HIV indicator conditions (HIV ICs) and strongest associations of ICs with HIV infection

A list was compiled of over 110 HIV ICs and symptoms reported across 42 studies which included approximately 105,500 HIV positive patients either prior to or after receiving a diagnosis of HIV. These studies were carried out across different healthcare settings (Table 1). The most commonly reported HIV-related conditions were; pneumonia and bacterial pneumonia (24 studies), herpes zoster (17 studies), oral candidiasis and oesophageal candidiasis (14 studies), STIs (in general) (14 studies), seborrhoeic dermatitis (12 studies), tuberculosis and pulmonary tuberculosis (8 studies), Kaposi sarcoma (8 studies), blood dyscrasia (7 studies) and thrombocytopenia (7 studies). The most common symptoms were diarrhoea (11 studies), fever/pyrexia (14 studies), weight loss (14 studies), and lymphadenopathy (17 studies).

The healthcare setting in which the HIV ICs were identified is an important factor when considering the prevalence of each condition/disease. Some diseases are more likely to be diagnosed and treated in the primary care setting e.g. herpes zoster. However, compared to patients seen in general practice, those who need to be hospitalised are likely to present with more complex conditions associated with immunosuppression. Figs. 1 to 7 show some of the most commonly reported HIV ICs and the prevalence estimates reported for each IC by healthcare setting (primary, secondary or tertiary care), using studies with available data.

To present results of our review of the most common reported HIV ICs we have grouped diseases into symptoms seen in PHI/AHI, STIs and blood borne viruses (BBVs), conditions associated with immunosuppression and cancers and finally other common conditions and symptoms.

3.1.2.1 Primary HIV infection

In the studies that analysed patients with PHI or AHI, the most commonly reported conditions/symptoms were fever/pyrexia of unknown origin, lymphadenopathy, rash, headache, weight loss and gastrointestinal symptoms (nausea, vomiting, diarrhoea). Lymphadenopathy was a condition commonly found in individuals reported as having PHI or AHI [25-28]. Strong associations of the presence of lymphadenopathy with PHI/AHI were reported in the following review articles; lymphadenopathy was present in 7-75% of patients with AHI [27], odds ratio of early HIV infection (versus uninfected) in those reporting lymphadenopathy was 4.6 (95% CI 1.3-8) and the presence of lymphadenopathy was the most useful sign to indicate an individual with early HIV infection [28]. Other studies also showed that lymphadenopathy or swollen glands were common symptoms in individuals with PHI: 45% [25] and 21% [26].

Fever/pyrexia was also a commonly reported symptom in PHI or AHI; in individuals infected with HIV (91% were MSM) 55% had reported symptoms of fever [26] and among patients with AHI it was 77% [29]. In a review article by Richey & Halperin (2013), between 53-90% of patients presented with fever and in a multivariable analysis of individuals with PHI, fever (OR 5.2, 95% CI 2.3-11.7) and rash (OR 4.8, 95% CI 2.4-9.8) were the symptoms most strongly associated with PHI and indicated the highest risk of HIV infection [30]. Other conditions and symptoms commonly seen in individuals with PHI /AHI are listed in Table 1 alongside the study references.

3.1.2.2 Sexually transmitted infections (STIs) and Blood Born viruses (BBVs)

STIs and BBVs most commonly reported either prior to or at HIV diagnosis were; Hepatitis C (9 studies), Hepatitis B (8 studies), syphilis (7

studies), condyloma acuminata (3 studies), gonorrhoea (3 studies), chlamydia (3 studies) and cytomegalovirus (2 studies). In studies reporting specific STIs, those with the highest prevalence in HIV positive individuals were syphilis, gonorrhoea and chlamydia. In addition, 14 studies reported STIs being associated with HIV infection, but did not report specific STIs.

Syphilis was a common STI found in individuals with HIV infection, present in 38% of HIV infected patients in Tokyo [31], 11% of MSM living with HIV [32] and 11% of individuals newly diagnosed with HIV in an Italian cohort study [33]. Gonorrhoea was also a common STI found in 27% of those newly diagnosed with HIV from a London HIV clinic [34] and 67 cases of gonorrhoea were reported prior to diagnosis in 1735 (3.8%) HIV infected individuals [33]. In a case control study of general practice databases in Amsterdam, gonorrhoea and syphilis were strongly associated with HIV infection OR 15.9, 95% CI 2.0 to infinity and OR 39.3 95% CI 5.7 to 1703.9 respectively [35]. Hepatitis B (HBV) and hepatitis C (HCV) were common BBVs diagnosed in individuals with HIV infection, among patients in Tokyo 18.9% had HBV [31], and in a primary care setting in Toronto among MSM 49.4% and 10.4% had HBV and HCV infection respectively [32]. Scognamiglio et al. found that there were 210 cases of viral hepatitis infections prior to diagnosis in 1735 (12%) individuals newly diagnosed with HIV infection. In a case control study identifying ICs for HIV infection diagnosed within hospital settings, strong associations were seen for hepatitis A (aOR 41.6 95% CI 11.7-148), non-A viral hepatitis (aOR 23.6, 95% CI 16.5-33.7), STIs and viral hepatitis (aOR 12.3 95% CI 9.60 -15.7) and syphilis (aOR 94.7, 95% CI 20.9-429) [36].

A nationwide population-based cohort study encompassing all Danish residents aged 20-60 years during a 19-year study period estimated the five-year risk of an HIV diagnosis (FYRHD) after a first-time diagnosis of 147 pre-specified potential indicator diseases [37]. The study showed that a number of diseases were identified with a FYRHD >0.1% including infectious diseases such as syphilis and hepatitis which were associated with particularly high FYRHD. Other STIs and BBVs commonly seen in individuals with HIV infection are shown in Table 1 alongside the study references.

3.1.2.3 Conditions associated with immuno-suppression and cancer

The most commonly reported conditions associated with immunosuppression and cancers in individuals with HIV infection were; pneumonia (24 studies), oral/oesophageal candidiasis (14 studies), Kaposi sarcoma (8 studies), cervical dysplasia and cervical cancer (7 studies), lymphoma and Non-Hodgkins Lymphoma (NHL) (4 studies) and wasting syndrome (3 studies).

Pneumonia was a common condition associated with immunosuppression found in HIV infected individuals. Bacterial pneumonia was reported in 4% of HIV infected patients in a retrospective case note review in primary and secondary care settings [38] and in 8% of patients in a service evaluation of four general practices in London [39]. In a UK case control study of patients in general practices that used data from the health improvement network (THIN) database bacterial pneumonia and oral candidiasis were most strongly associated with HIV infection (OR 47.7, 95% CI 5.6 to 404.2 and OR 29.4 95% CI 6.9 to 125.5, respectively) [40]. The percentage prevalence of pneumocystis jiroveci pneumonia (PJP) in HIV infected individuals across primary, secondary and tertiary care settings ranged from 9 to 29% (Fig. 1) with the highest prevalence in secondary care settings estimated from two separate studies of newly HIV infected individuals from retrospective reviews of patient medical records [20,41].

Kaposi sarcoma (Fig. 2) was a common cancer associated with immunosuppression seen among HIV positive patients in primary care [39], secondary care [31,42,43], secondary and tertiary setting [44,45] and across all 3 settings [46].

Oral /oesophageal candidiasis and wasting syndrome were also frequently reported conditions seen either prior to or after an HIV positive diagnosis. A large retrospective study of newly infected adults in Sweden found candida oesophagitis and wasting syndrome to be the most common AIDS defining conditions [17]. In HIV infected late presenters (presenting with AIDS defining illness and/or CD4 counts of <350 cells/µl) in Germany, 51% reported symptoms of candida oesophagitis and 40% with wasting syndrome [20]. Oral candidiasis was reported as a common condition in 4 studies [35,39,47,48] and oesophageal candidiasis in 5 studies [31,47, 49-51].

Table 1. Studies showing the most commonly reported HIV indicator conditions (HIV ICs) found in HIV positive individuals and IC(s) associated with HIV infection alongside the corresponding study references

HIV Indicator Conditions (ICs) and signs and symptoms	Individual prevalence (%) & prevalence ranges (%) of IC(s) in HIV+ individuals‘ across different studies	Studies showing most common HIV IC(s) found in HIV+ individuals & IC(s) associated with HIV infection	
		IC(s) presenting in individuals with general HIV infection	IC(s) presenting in individuals with PHI or AHI
Symptoms seen in Primary HIV infection (PHI)			
Acute Retroviral syndrome/acute HIV infection (AHI)	1 to 28%	Liggett et al 2016, Sacks et al 2017	
Primary HIV Infection (PHI)	4.4 to 4.5%	Dorward et al 2012, Brannstrom et al 2016	
Mononucleosis- like illness	1.7%	Joore et al 2015, Menacho et al 2013*, Rayment et al 2012*, Sullivan et al 2013*, Wellesley et al 2015*, Wohlgemut et al 2012*, Ellis et al 2012, Lexton & Cunningham 2017*	
Fever and Pyrexia of unknown origin	2 to 8% (general HIV infection) 53 to 90% (PHI /AHI)	Champenois et al 2013, Chin et al 2013, Klein et al 2003, Joore et al 2015, Horino et al 2016, Cropp et al 2015, Damery et al 2013, Dorward et al 2012, Wohlgemut et al 2012	Braun et al 2015, Hecht et al 2002*, Hoenigl et al 2016, Richey & Halperin 2013, Sudarshi et al 2008
Lymphadenopathy	2 to 7 % (general HIV infection) 7 to 75% (PHI/ AHI)	Brawley et al 2013, Champenois et al 2013, Chin et al 2013, Ellis et al 2012, Horino et al 2016, Joore et al 2015, Klein et al 2003, Liggett et al 2016*, Rivero Marcotegui et al 2014, Rayment et al 2012*, Dorward et al 2012, Wellesley et al 2015*, Wohlgemut et al 2012*	Braun et al 2015, Sudarshi et al 2008, Richey & Halperin 2013, Wood et al 2014*
Night sweats	2.6% (general HIV infection) 55% (PHI/AHI)	Klein et al 2003, Liggett et al 2016*	Hoenigl et al 2016
Opportunistic diseases	23%		Braun et al 2015
Gastrointestinal symptoms (nausea, vomiting, diarrhoea)	14- 68%		Braun et al 2015, Hoenigl et al 2016, Sudarshi et al 2008, Richey & Halperin 2013, Wood et al 2014*
Neurological symptoms	12%		Braun et al 2015
Skin soft tissue symptoms	9%		Braun et al 2015
Respiratory symptoms	6%		Braun et al 2015
Urogenital symptoms	3%		Braun et al 2015
Fatigue	26 to 90%		Hoenigl et al 2016, Richey & Halperin 2013
Elevated liver enzymes	61%		Braun et al 2015
Pharyngitis[abc], Flu like symptoms, [d] Sore throat[d], Cough[a]	15 to 70%		Braun et al 2015[a], Hoenigl et al 2016[b], Richey & Halperin 2013[c], Sudarshi et al 2008[d]
Oral ulcers	12 to 20%		Braun et al 2015, Richey & Halperin 2013

HIV Indicator Conditions (ICs) and signs and symptoms	Individual prevalence (%) & prevalence ranges (%) of IC(s) in HIV+ individuals‘ across different studies	Studies showing most common HIV IC(s) found in HIV+ individuals & IC(s) associated with HIV infection	
		IC(s) presenting in individuals with general HIV infection	IC(s) presenting in individuals with PHI or AHI
Weight loss	22 -76%		Braun et al 2015, Hoenigl et al 2016, Richey & Halperin 2013, Wood et al 2014*
Respiratory			
Respiratory tract infections	10.6 to 12%	Chin et al 2013, Jenkins et al 2006, Sogaard et al 2012*	
Recurrent bacterial infections	1 to 9%	Champenois et al 2013, Chin et al 2013	
Pulmonary diseases	Not reported	Omland et al 2016*	
Tuberculosis /Pulmonary tuberculosis	0.6 to 5.5%	Horino et al 2016, Ramasami et al 2012, Rivero Marcotegui et al 2014, Scognamiglio et al 2013, Valentini et al 2015, Wohlgemut et al 2012*, Raben et al 2015*, Liggett et al 2016*	
Endocarditis	Not reported	Sogaard et al 2012*, Omland et al 2016*	
Neurology			
CNS toxoplasmosis	0.2 to 8%	Chin et al 2013, Mugavero et al 2007, Horino et al 2016, Wohlgemut et al 2012*, Tominski et al 2016, Valentini et al 2015	
CNS infection	Not reported	Sogaard et al 2012*	
Cryptococcal meningitis	0.4 to 4.4%	Chin et al 2013, Horino et al 2016, Mugavero et al 2007,	
HIV related encephalopathy	0.7%	Horino et al 2016, Lexton & Cunningham 2017*	
Progressive multifocal leukoencephalopathy	0.2 to 1%	Horino et al 2016, Mugavero et al 2007	
Peripheral neuropathy	3.9%	Joore et al 2015, Wohlgemut et al 2012*	
Facial nerve disorder & Neuropathy	Not reported	Omland et al 2012*	
Dementia	0.9%	Dorward et al 2012	
Headache	Not reported (general HIV infection) 11 to 70% (PHI/AHI)	Liggett et al 2016*	Braun et al 2015, Sudarshi et al 2008, Hoenigl et al 2016, Richey & Halperin 2013
Skin			
Herpes zoster/ Varicella zoster	1.3 to 9%	Agusti et al 2016*, Brannstrom et al 2016*, Damery et al 2013*, Horino et al 2016, Jenkins et al 2006, Joore et al 2015, Klein et al 2003, Rivero Marcotegui et al 2014, Menacho et al 2013*, Read et al 2011*, Sogaard et al 2012*, Sullivan et al 2013*, Tominski et al 2016, Wellesley et al 2015*, Wohlgemut et al 2012*, Omland	

HIV Indicator Conditions (ICs) and signs and symptoms	Individual prevalence (%) & prevalence ranges (%) of IC(s) in HIV+ individuals‘ across different studies	Studies showing most common HIV IC(s) found in HIV+ individuals & IC(s) associated with HIV infection	
		IC(s) presenting in individuals with general HIV infection	IC(s) presenting in individuals with PHI or AHI
		et al 2016*, Champenois et al 2013	
Herpes simplex	0.7%	Horino et al 2016, Omland et al 2016*, Liggett et al 2016*	
Seborrhoeic dermatitis/ severe seborrhoeic dermatitis and Seborrhoeic exanthema	1 to 4.2%	Brannstrom et al 2016, Klein et al 2003, Rivero Marcotegui et al 2014, Scognamiglio et al 2013, Sullivan et al 2013*, Wellesley et al 2015*, Wohlgemut et al 2012*, Dorwood et al 2012, Ellis et al 2012, Gullon et al 2016*, Menacho et al 2013*, Joore et al 2015	
Soft tissue infections/skin infections	8.6%	Jenkins et al 2006, Sogaard et al 2012*	
Psoriasis or severe psoriasis	1%	Dorward et al 2012*, Wohlgemut et al 2012*, Joore et al 2015	
Skin lesions	4.6%	Horino et al 2016	
Rash	9 to 80%		Braun et al 2015, Sudarshi et al 2008, Hoenigl et al 2016, Hecht et al 2002*, Richey & Halperin 2013
Molluscum contagiosum	0.4%	Horino et al 2016, Read et al 2011*	
Erythema multiforme	0.2%	Horino et al 2016	
Scabies	0.2%	Horino et al 2016	
Dermatological infections	4.9%	Jenkins et al 2006	
Blood			
Haematological disorders	1.5%	Rivero Marcotegui et al 2014, Sogaard et al 2012*	
Leukocytopenia	2.9 to 24%	Rayment et al 2012*, Joore et al 2015, Tominski et al 2016	
Leukopenia	40%		Richey & Halperin 2013
Blood Dyscrasia	4 to 21.5%	Brannstrom et al 2016*, Brawley et al 2013, Ellis et al 2012, Walker et al 2015*, Whittle et al 2013, Wellesley et al 2015*, Dorwood et al 2012	
Thrombocytopenia	0.9 to 22%	Cropp et al 2015, Horino et al 2016, Rayment et al 2012*, Sogaard et al 2012*, Tominski et al 2016, Wohlgemut et al 2012*, Omland et al 2016*	Braun et al 2015
Hypergammaglobulinemia	1.5%	Horino et al 2016	
Leukopenia/Thrombopenia	Not reported	Menacho et al 2013*, Sullivan et al 2013*	
Lymphopenia/Neutropenia	Not reported	Read et al 2011*, Wohlgemut et al 2012*	
Co- infection with other BBVs	1.4%	Cropp et al 2015	
Gastroenterology			

HIV Indicator Conditions (ICs) and signs and symptoms	Individual prevalence (%) & prevalence ranges (%) of IC(s) in HIV+ individuals‘ across different studies	Studies showing most common HIV IC(s) found in HIV+ individuals & IC(s) associated with HIV infection	
		IC(s) presenting in individuals with general HIV infection	IC(s) presenting in individuals with PHI or AHI
Gastrointestinal diseases	Not reported	Omland et al 2016*	
Candida infection	Not reported	Sogaard et al 2012*	
Herpetic esophagitis	0.6%	Rivero Marcotegui et al 2014	
Oral hairy leucoplakia	0.9%	Wohlgemut et al 2012*, Dorward et al 2012	
Oral infection	2.6%	Klein et al 2003	
Weight loss	1.3 to 8.8%	Brawley et al 2013, Damery et al 2013*, Brannstrom et al 2016, Ellis et al 2012, Joore et al 2015, Liggett et al 2016*, Walker et al 2015*, Wellesley et al 2015*, Champenois et al 2013, Dorward et al 2012, Klein et al 2003, Rivero Marcotegui et al 2014, Tominski et al 2016, Wohlgemut et al 2012*,	
Diarrhoea & chronic diarrhoea	1 to 9%	Brawley et al 2013, Ellis et al 2012, Gullon et al 2016*, Rivero Marcotegui et al 2014, Wellesley et al 2015*, Wohlgemut et al 2012*, Champenois et al 2013, Damery et al 2013*, Liggett et al 2016*, Walker et al 2015*, Joore et al 2015	
Cryptosporidiosis	0.2 to 1%	Horino et al 2016, Mugavero et al 2007	
Sexually transmitted infections (STIs)			
STIs (general)	3.6 to 29%	Brannstrom et al 2016, Champenois et al 2013, Ellis et al 2012, Gullon et al 2016*, Jenkins et al 2006, Rivero Marcotegui et al 2014, Sogaard et al 2012*, Wellesley et al 2015*, Wohlgemut et al 2012*, Arkell et al 2011*, Dorward et al 2012, Lexton & Cunningham 2017*, Joore et al 2015, Scognamiglio et al 2013	
Hepatitis	Not reported	Brannstrom et al 2016*, Omland et al 2016*	
Non-A viral hepatitis	Not reported	Sogaard et al 2012*, Omland et al 2016*	
Hepatitis A	Not reported	Sogaard et al 2012*, Omland et al 2016*	
Hepatitis B	2.2 to 7.3%	Horino et al 2016, Rivero Marcotegui et al 2014, Rayment et al 2012*, Scognamiglio et al 2013, Sullivan et al 2013*, Wohlgemut et al 2012*, Raben et al 2015*, Joore et al 2015	
Hepatitis C	1.4 to 4.8%	Agusti et al 2016*, Rivero Marcotegui et al 2014, Rayment et al 2012*, Read et al 2011*, Scognamiglio et al 2013, Sullivan et al 2013*, Wohlgemut et al 2012*, Raben et al 2015*, Sacks et al 2017	

HIV Indicator Conditions (ICs) and signs and symptoms	Individual prevalence (%) & prevalence ranges (%) of IC(s) in HIV+ individuals‘ across different studies	Studies showing most common HIV IC(s) found in HIV+ individuals & IC(s) associated with HIV infection	
		IC(s) presenting in individuals with general HIV infection	IC(s) presenting in individuals with PHI or AHI
Syphilis	4.4 to 13%	Agusti et al 2016*, Horino et al 2016, Joore et al 2015, Scognamiglio et al 2013, Sogaard et al 2012*, Omland et al 2016*, Sacks et al 2017	
Chlamydia	10.8 to 14.9%	Joore et al 2015, Lexton & Cunningham 2017*, Sacks et al 2017	
Cytomegalovirus infection	0.9 to 2%	Horino et al 2016, Mocroft et al 2013	
Amebic disease	2.1%	Horino et al 2016	
Condyloma acuminata	2.1 to 3.9%	Horino et al 2016, Joore et al 2015, Omland et al 2016*	
Gonorrhoea	3.9 to 26.6%	Joore et al 2015, Scognamiglio et al 2013, Sacks et al 2017	
Human papilloma virus related disease	Not reported	Read et al 2011*	
Genital warts	4.9%	Scognamiglio et al 2013	
Genital ulcers	3%		Braun et al 2015, Wood et al 2014*
Genital herpes	1 to 1.9%	Joore et al 2015, Scognamiglio et al 2013	
Infectious vaginitis	0.1%	Scognamiglio et al 2013	
GYN/STD/GU complaints	14%	Liggett et al 2016	
Nonspecific symptoms			
Fatigue	2.4%	Brannstrom et al 2016, Liggett et al 2016*	
Sore throat	Not reported	Liggett et al 2016*	
Arthropathy	Not reported	Liggett et al 2016*	
Myalgia	18 to 70%		Hoenigl et al 2016, Braun et al 2015, Richey & Halperin 2013
Arthralgia	12 to 70%		Braun et al 2015, Sudarshi et al 2008, Hoenigl et al 2016, Richey & Halperin 2013
Chills	Not reported	Liggett et al 2016*	
Anorexia	Not reported	Liggett et al 2016*	
Conjunctivitis	Not reported	Liggett et al 2016*	
Nausea	Not reported	Liggett et al 2016*	
Near syncope	Not reported	Liggett et al 2016*	
Kidney			
HIV associated nephropathy	2.2%	Ramasami et al 2012	
Conditions associated with immunosuppression & Cancers			

HIV Indicator Conditions (ICs) and signs and symptoms	Individual prevalence (%) & prevalence ranges (%) of IC(s) in HIV+ individuals‘ across different studies	Studies showing most common HIV IC(s) found in HIV+ individuals & IC(s) associated with HIV infection	
		IC(s) presenting in individuals with general HIV infection	IC(s) presenting in individuals with PHI or AHI
Bacterial pneumonia	0.7 to 16.9%	Brawley et al 2013, Cropp et al 2015, Damery et al 2013*, Dorward et al 2012, Valentini et al 2015, Whittle et al 2013, Wellesley et al 2015*, Wohlgemut et al 2012*, Arkell et al 2011*, Liggett et al 2016*	
Pneumococcal pneumonia	Not reported	Omland et al 2016*	
Pneumonia & recurrent pneumonia	3.4 to 8%	Joore et al 2015, Klein et al 2003, Rayment et al 2012*, Read et al 2011*, Brannstrom et al 2016*	
Pneumocystis jiroveci pneumonia	9 to 29%	Chin et al 2013, Horino et al 2016, Mocroft et al 2013, Mugavero et al 2007, Ramasami et al 2012, Valentini et al 2015, Walker et al 2015, Dorward et al 2012*, Liggett et al 2016*, Tominski et al 2016, Brannstrom et al 2016*, Wohlgemut et al 2012*, Lexton & Cunningham 2017*	
Oral /oesophageal candidiasis/ Candida oesophagitis	0.6 to 44%	Liggett et al 2016*, Tominski et al 2016, Raben et al 2015*, Brannstrom et al 2016, Valentini et al 2015 Damery et al 2013*, Dorward et al 2012, Horino et al 2016, Rivero Marcotegui et al 2014, Wellesley et al 2015*, Wohlgemut et al 2012*, Mocroft et al 2013, Chin et al 2013, Joore et al 2015	
Wasting syndrome/ AIDS wasting syndrome	3.4 to 39.6%	Brannstrom et al 2016, Tominski et al 2016, Liggett et al 2016*	
Cytomegalovirus esophagitis	Not reported	Liggett et al 2016*	
Ocular toxoplasmosis	Not reported	Liggett et al 2016*	
Toxoplasmosis of the hand	Not reported	Liggett et al 2016*	
Mycobacterium avium complex	1%	Chin et al 2013	
Cytomegalovirus (CMV) infection	0.9 to 13.9%	Horino et al 2016, Mocroft et al 2013	
CMV retinitis	Not reported	Liggett et al 2016*, Wohlgemut et al 2012*	
Progressive multifocal leukoencephalopathy	0.2 to 1%	Horino et al 2016, Mugavero et al 2007	
Cancers			
Lymphoma & Non-Hodgkin’s Lymphoma	0.8 to 1.8%	Horino et al 2016, Mugavero et al 2007, Sullivan et al 2013*, Raben et al 2015*	
Cervical dysplasia, Cervical intra-epithelial neoplasia stage III, Cervical carcinoma in situ/ Cervical cancer	0.6 to 1.5%	Brannstrom et al 2016*, Sullivan et al 2013*, Tominski et al 2016, Lexton & Cunningham 2017*, Rivero Marcotegui et al 2014, Raben et al 2015*, Joore et al	

HIV Indicator Conditions (ICs) and signs and symptoms	Individual prevalence (%) & prevalence ranges (%) of IC(s) in HIV+ individuals[ᵠ] across different studies	Studies showing most common HIV IC(s) found in HIV+ individuals & IC(s) associated with HIV infection	
		IC(s) presenting in individuals with general HIV infection	IC(s) presenting in individuals with PHI or AHI
		2015	
Anal cancer	Not reported	Brannstrom et al 2016*, Sullivan et al 2013*	
Kaposi sarcoma	0.9 to 3.3%	Liggett et al 2016*, Dorward et al 2012, Wohlgemut et al 2012*, Lexton & Cunningham 2017* Dorward et al 2012*, Horino et al 2016, Mugavero et al 2007, Ramasami et al 2012	

ᵠ IC(s) identified in individuals before or after receiving a HIV positive diagnosis and includes studies carried out across different healthcare settings (e,g primary, secondary and tertiary care settings)
** % prevalence of IC(s) not included in prevalence range figures in Table 1 as data either not reported or available from the study, or the IC(s) were reported as number of episodes/ number of consultations related to the IC(s) itself or frequency of IC(s) only reported as odds ratios and confidence intervals. PHI: Primary HIV Infection, AHI: Acute HIV Infection*

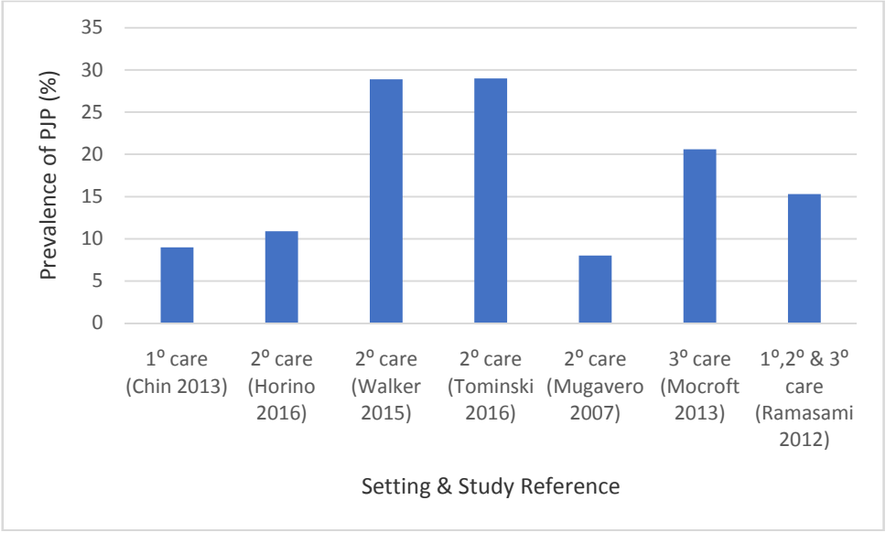

Fig. 1. Prevalence of pneumocystis jiroveci pneumonia (PJP) in HIV + individuals across different healthcare settings
1° care: primary care setting, 2° care: secondary care setting, 3° care: tertiary care setting

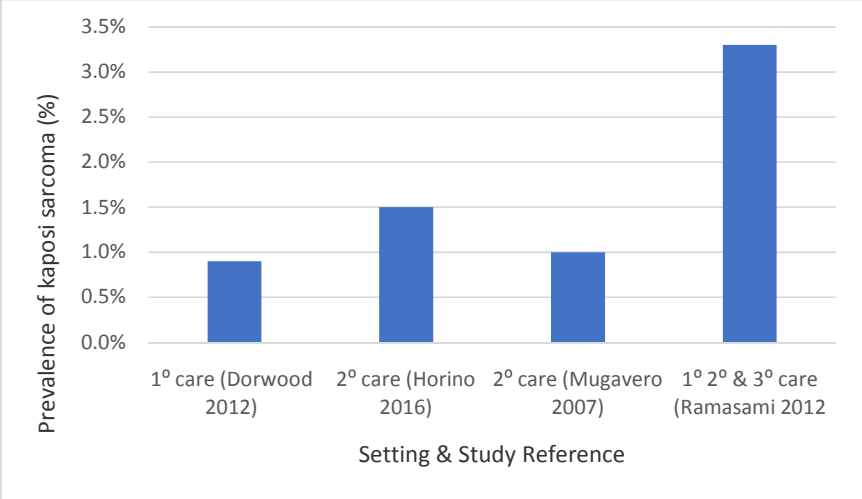

Fig. 2. Prevalence of Kaposi sarcoma in HIV+ individuals across different healthcare settings
1 ^{0} care: primary care setting, 2 ^{0} care: secondary care setting, 3 ^{0} care: tertiary care setting

3.1.2.4 Other common conditions & symptoms

Other conditions and symptoms commonly reported were blood dyscrasias with prevalence in HIV infected individuals of 5% in primary care [39], 4% in primary and secondary care [38] and 6.4% in tertiary care [52]. Specifically, thrombocytopenia was a common blood disorder reported in HIV infected individuals across all settings [20,31,36,44,53,54]. The prevalence of seborrhoeic dermatitis in HIV infected individuals ranged from 1% to 2.7% in primary care [35,39], 4.2% in secondary care [47] and 2.1% [33] and 2.6% [48] in tertiary care (Fig. 3). Herpes zoster was also commonly reported in HIV positive patients, with a prevalence of 6.9% in a primary care study [35], 1.3% [31] ,9% [20] and 5.5% [47] in secondary care settings and 4.6% in a tertiary care setting [48] (Fig. 4).

Tuberculosis or pulmonary tuberculosis were observed in 5 studies investigating HIV ICs in HIV positive patients, with prevalence ranging from 0.6% to 5.5% across different healthcare settings (Fig. 5). Weight loss and diarrhoea were also very common symptoms and reported in many studies investigating HIV ICs in HIV positive patients prior to or after diagnosis. The

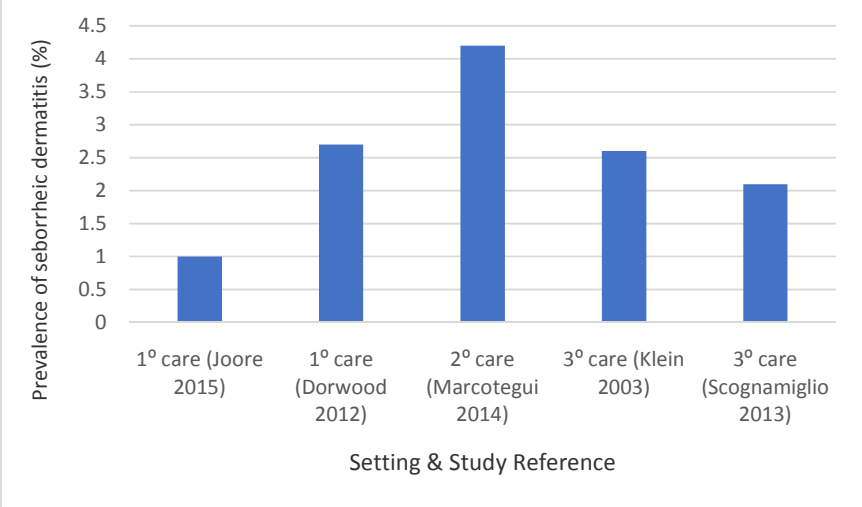

Fig. 3. Prevalence of seborrheic dermatitis in HIV+ individuals across different healthcare settings
1 ^{0} care: primary care setting, 2 ^{0} care: secondary care setting, 3 ^{0} care: tertiary care setting

prevalence of weight loss ranged from 1.3 to 8.8% (not including individuals with PHI/AHI) (Fig. 6) with the highest prevalence observed in a case control study in Amsterdam from a general practice database showing a strong association with HIV infection (OR 39, 95% CI 2.0 to infinity) [35]. In addition, the THIN study showed a strong association between weight loss and HIV-infection (OR 13.4, 95% CI 5.0 to 36) [40].

Prevalence of diarrhoea in HIV infected individuals ranged from 1% to 9% (Fig. 7) with the highest prevalence observed in tertiary care settings of newly diagnosed HIV patients, from retrospective audits of HIV centres in the UK [52] and from a French national agency for research on AIDS and viral hepatitis cohort (ANRS) [14].

The nationwide population study of Danish residents estimating FYRHD after a first-time diagnosis of 147 HIV ICs [37] found that endocarditis, several pulmonary vascular diseases and haematological diseases (particularly in males) (e.g thrombocytopenia) were also associated with an FYRHD >0.1%. Gastrointestinal disease in older males, and

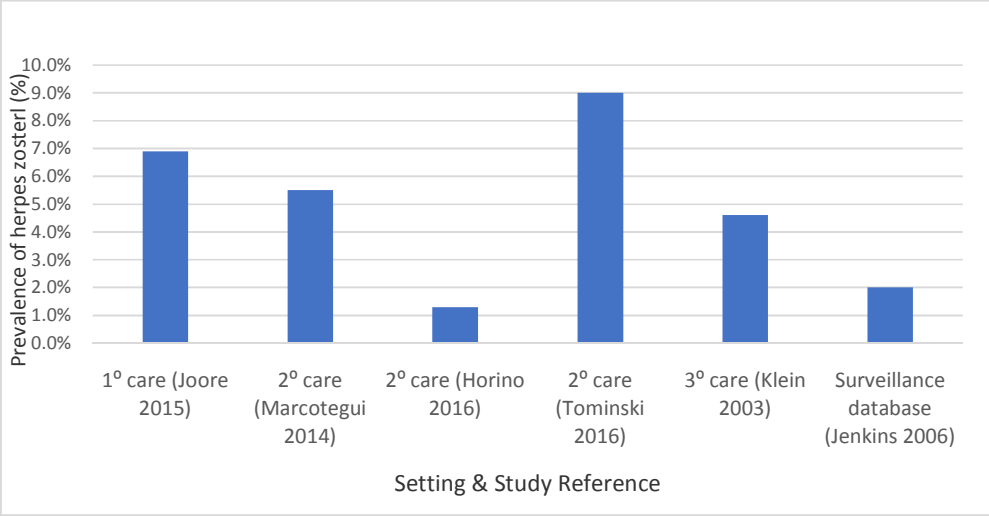

Fig. 4. Prevalence of herpes zoster in HIV+ individuals across different healthcare settings
1 ^{0} care: primary care setting, 2 ^{0} care: secondary care setting, 3 ^{0} care: tertiary care setting

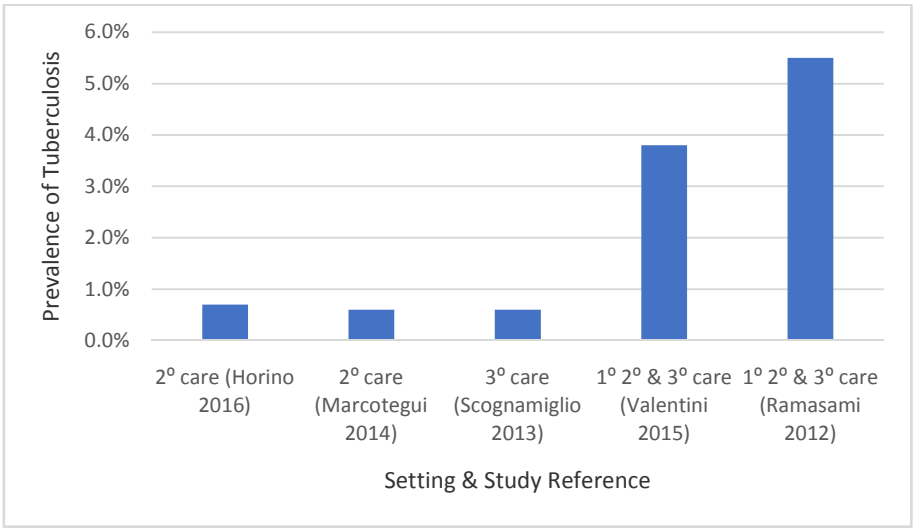

Fig. 5. Prevalence of Tuberculosis in HIV+ individuals across different healthcare settings
1 ^{0} care: primary care setting, 2 ^{0} care: secondary care setting, 3 ^{0} care: tertiary care setting

facial nerve disorder and neuropathy in males were associated with an FYRHD >0.1%.

3.2 Interventions Using HIV ICs to Guide HIV Testing and Case Finding

3.2.1 Characteristics of the studies

We found 12 intervention studies that had used HIV ICs as markers or flags either in isolation or alongside other risk factors to guide HIV testing and case finding (Table 2). Studies are presented in reverse chronological order with the most recent study at the top of the table. The table shows for each study: reference and location, study design, intervention & comparison, target population, number or percentage with ICs, HIV test rate, number/rate of HIV positive diagnoses and a description of the main study objectives and outcomes.

Articles describing studies included ten peer reviewed papers and two abstracts from BHIVA conference proceedings (n=2). Locations of included studies were as follows; within Europe including the UK (n=2), Spain (n=3), Belgium

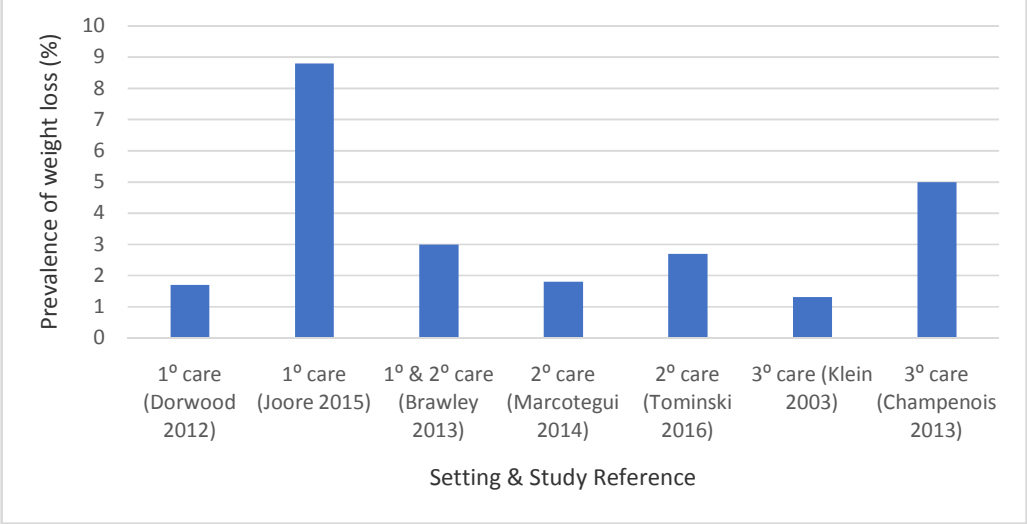

Fig. 6. Prevalence of weight loss in HIV+ individuals across different healthcare settings
1 ^{0} care: primary care setting, 2 ^{0} care: secondary care setting, 3 ^{0} care: tertiary care setting

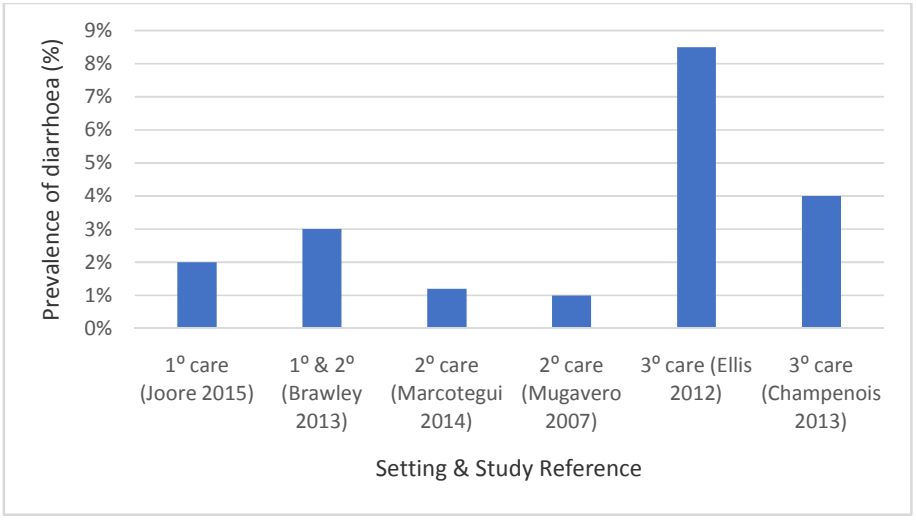

Fig. 7. Prevalence of diarrhoea in HIV+ individuals across different healthcare settings
1 ^{0} care: primary care setting, 2 ^{0} care: secondary care setting, 3 ^{0} care: tertiary care setting

(n=1), and the USA (n=6), which included Colorado (n=1), Connecticut (n=1), Chicago (n=1), Washington state (n=1), and multiple cities across USA (n=2). The types of interventions included: electronic clinical decision support system & clinical reminders (n=4), risk prediction tools (n=3), training sessions on ICs and participation in the HIDES study (n=1), education sessions alongside case note prompts of patients with ICs (n=1), rapid HIV testing based on presence of an IC (n=2) and HIV risk exposure and IC questionnaire to support targeted screening (n=1). These studies took place in the following settings, primary care (n=3), secondary care (n=2), primary care centres and emergency department (n=1), primary and secondary care settings (n=1), STD clinics (n=2), Veterans affairs healthcare system (n=2), high risk participants from the HIV Network for prevention Trials (HIVNET) Vaccine Preparedness study (n=1).

3.2.2 Effectiveness of Interventions using HIV ICs to guide HIV testing

The majority of studies showed that interventions using HIV ICs to guide testing were successful in increasing testing rates and the number of HIV positives identified (Table 2). Federman et al. assessed the effectiveness of an electronic clinical reminder added to the medical records within the Veteran's affairs (VA) healthcare system in the USA [55]. The reminder was based on risk factors for HIV (high risk sexual behaviour, alcohol or substance use disorders) as well as hepatitis and other sexually transmitted diseases (STDs). Testing based on the use of the reminder led to the diagnosis of HIV in 24 patients over a 19-month period and testing increased by 369%. Another study based in the USA by Schrantz et al (2011), developed a web based patient tracking software to flag selected patients for testing. Selection criteria included presenting with STIs, pregnancy, symptoms of an HIV IC, bacterial pneumonia (in <65-year olds), people who inject drugs (PWID) and MSM. The study showed a strong association between the use of the system and a 262% increase in testing frequency (from 29.6 to 80.5 tests per month) [56].

An intervention developed by Goetz et al (2008) using a clinical reminder triggered by prior evidence of hepatitis B or C, STDs (gonorrhoea, chlamydia, syphilis or genital herpes) with other behavioural risk factors (e.g drug use) showed that the use of clinical reminders increased the frequency of testing and the number of new diagnoses made. They tested the intervention in five veterans' healthcare administration facilities (2 intervention, 3 controls). At the two intervention sites testing increased from 4.8% to 10.8% and 5.5% to 12.8% with new HIV diagnoses doubling from 15 to 30 among at-risk individuals comparing the years pre-and post-intervention [57]. A later evaluation study found that the impact on HIV testing rates was fully sustainable and that providers became more proficient at offering and discussing HIV tests [58].

Branch et al., carried out a study to assess the feasibility and acceptability of an electronic clinical decision support system prompting HIV testing for use in hospital and general practice. An algorithm was devised so that when certain tests were selected (e.g hepatitis serology) a screen prompt would suggest also offering an HIV test. Evaluation interviews with the doctors and nurses conducted after a 3-month trial period found that the prompt was generally acceptable and was considered useful and educational. Nurses reported that they were less comfortable responding to the prompt in situations where they thought testing was not justified. However, only between 1% and 2% of all prompts were accepted by the HCP. No positive HIV tests resulted from the prompts, but the number of tests ordered increased by 6% in the primary care setting compared to the previous 9 months before the trial (p=0.165). This study is currently being developed further to refine the application to provide more accurate risk stratification [59].

Cayuelas-Redondo et al. undertook an intervention to raise awareness of IC guided HIV testing that consisted of training sessions and participation in the HIDES study in 3 primary care centres (PCCs). They analysed whether the intervention in this multicentre retrospective study influenced the proportion of HIV serology requested. The number of HIV tests in patients with an IC was 3.9% pre-intervention in 2008 and increased to 11.8% post-intervention in 2012 (P< .0001). The HIV infection rate was 2.2% (95% CI :0.4-7.3) (n=2). Although the requests for HIV tests tripled in number there were a further 88% of cases where a test should have been offered, and a further 25 new cases would have been diagnosed between 2008 and 2012 if a test had been offered to all patients with an IC [60].

Table 2. Interventions using HIV clinical indicators to increase HIV testing and increase case-finding (n=12)

Reference & Study location	Study Type and Intervention	Intervention /Comparison	Population targeted	No. or % with ICs, No. or % HIV+, HIV test rate	Main objective and outcome of study
Branch et al 2016 [59], UK (BHIVA abstract) (recently published paper: Chadwick et al 2017[85]	Feasibility study	Electronic clinical decision support system (CDSS)	Patients from 2 clinical settings (Chelsea & Westminster (C & W) Hospital & Teeside primary care	No HIV+ tests resulted from prompted requests, No. of tests ordered were 6% higher in the trial period in Teeside compared to the previous 9 months	**Objective:** to assess the feasibility of a prototype CDSS application prompting HIV testing based on Drs/Nurses selecting certain tests (e.g. when hepatitis serology selected). **Outcome:** The system was found to be both useable and acceptable to hospital doctors, GPs and nurses with little evidence of prompt/alert fatigue. In general practices, around 1 in 10 prompts were accepted and there was a 6% increase in testing rates over the 3-month study period (P=0.169)**.** Further development to include additional clinical data and refining application to provide more accurate risk stratification
Elias et al 2016 [63], Madrid, Spain	Prospective, one arm, open label study	HIV risk exposure and IC (HIV RE&IC) Questionnaire to support targeted HIV screening	Patients attending emergency room or PCC	Confirmed hidden HIV infection was detected in 4.1%, while HIV RE&IC was positive in 51.2%. 5329 valid paired HIV RE&IC Questionnaires and rapid HIV tests were performed. 3694 (69.3%) in the PCC	**Objective:** a feasibility study using an HIV risk exposure and indicator condition (HIV RE&IC) questionnaire to support targeted HIV screening. All enrolled patients filled out a questionnaire and were HIV tested. **Outcome:** The HIV RE&IC questionnaire sensitivity was 100% to predict HIV infection, with a 100% negative predictive value. When considered separately RE or IC items sensitivity decreases to 86.4% or 91% & NPP to 99.9% for both of them. Questionnaire accurately discriminated all non-HIV infected people without missing any HIV diagnoses
Cayuelas-Redondo et al 2015 [60], Spain	Multicentre retrospective review	Retrospective review was conducted comparing the baseline (3 primary care centres (PCC) in 2008) and a post-collaboration period (3 PCC in 2012). The collaboration consisted of training sessions and participation in the HIDES study	3 PCC in Spain involved in collaboration to raise awareness of early detection of HIV (HIDES study)	1219 ICs were included (558 in 2008 and 661 in 2012) In 2008: No. of HIV tests in patients with an IC was 3.9% and rose to 11.8% in 2012 (P< .0001). HIV infection rate was 2.2%. Estimated that 25 new cases (12 in 2008 and 13 in 2012) would have been diagnosed if test had been performed on all patients with ICs.	**Objective**: to analyse whether a collaboration to raise awareness of the importance of early detection of HIV in 3 primary care centres influenced the proportion of HIV serology requested. **Outcome:** Predictors of HIV request were having an IC in 2012, a younger age, having a mononucleosis syndrome and not being Spanish. The HIV request demand tripled after the collaboration with primary care centres, however in 88% of patients the test was not requested, resulting in diagnostic losses.

Reference & Study location	Study Type and Intervention	Intervention /Comparison	Population targeted	No. or % with ICs, No. or % HIV+, HIV test rate	Main objective and outcome of study
Dosekun et al 2013 [61], Brighton, UK (BHIVA abstract)	A two-stage prospective study	Clinicians received an education programme about significance of late HIV diagnosis, highlighting ICs relevant to their field. Stage 1 consisted of pre-identification of IC & insertion of a prompt to offer HIV test. Stage 2 relied on clinician identification of IC only (no prompt)	Patients attending outpatient clinic (Dermatology, Gastroenterology, Haematology) at 2 university hospitals. (4191 eligible patients)	Test offer and uptake rate was compared with/without prompts and across age, gender and ethnic groups. 608 (14.5%) identified to have ICs of whom 25 (4.1%) were HIV+. Overall test offer was 17.5% and was significantly higher during the prompt stage	**Objective:** to assess the impact of targeted outpatient clinics educational programme with and without additional individual case note prompts for patients with ICs as a strategy to increase HIV testing. **Outcome:** overall test offer was 17.5% and was significantly higher during the prompt stage (34%) vs education alone (3.1%) ($p<0.001$). Individual case note prompts significantly increased test offer rates
Gennotte et al 2013 [62], Belgium	Multicentre prospective study	Educational intervention based on presence of IC to prompt testing	GPs and patients in area of Brussels	29% had an IC, sero-prevalence was 1.5% among patients with an IC. The rate of new diagnoses was 0.5% for the rapid HIV test & 0.5% for the standard HIV test	**Objective:** to assess feasibility and acceptability of HIV screening through rapid tests to both GPs and patients. 10 GPs were trained in rapid HIV testing in area of Brussels with a substantial African community. One of the inclusion criteria being presence of ICs as defined by HIDES, to determine the number of new HIV infections diagnosed among tested patients. **Outcome:** Drs assessment: greater understanding of and ease in performing the testing procedure after 6 months of training support than after just 1 month. GPs felt more comfortable offering a test based on risk or the presence of IC and more comfortable performing the test. Both standard and rapid tests were well received by patients but were usually not offered due to time constraints
Menacho et al 2013 [24], Barcelona, Spain	Multicentre prospective study	Compared prospectively IC guided testing (4 preselected ICs) versus testing of those with non-ICs (NIC)	Patients aged 18 to 65yrs attending 4 PCCs in Barcelona, Spain	During study period 775 patients attended with one of the 4 selected ICs and 66,043 presented with NIC. HIV screening was offered to 89 patients with ICs (offer rate 11.5%) of whom 100% completed testing. In the NIC group a test was offered to 344 (offer rate 5.2%) of whom 97% completed testing. 4 HIV+ tests	**Objective:** to compare prospectively IC guided testing versus testing of those with non-ICs using rapid finger- stick test, 4 ICs were selected these included: new herpes zoster infection, seborrheic eczema, mononucleosis syndrome or leukopenia /thrombocytopenia. **Outcome:** prevalence of HIV in IC group was 4.7% (95% CI: 1.3-11.6%) and in NIC group was 0.3% (95% CI 0.01-1.82 $P<0.009$). Although number of patients in study was small, IC guided HIV testing, based on 4 selected ICs, in PCCs seems to be a more feasible and less expensive strategy to improve diagnosis of HIV infection in Spain than a nontargeted HIV testing strategy.

Reference & Study location	Study Type and Intervention	Intervention /Comparison	Population targeted	No. or % with ICs, No. or % HIV+, HIV test rate	Main objective and outcome of study
				in IC group and 1 HIV+ in NIC group	
Haukoos et al 2012 [64], Denver, Colorado	Analysis of large, prospectively collected data	Clinical prediction tool to categorise patients into risk groups of HIV infection	Patient data from a metropolitan STD clinic	The derivation sample consisted of 92,635 patients of whom 504 (0.54%) were diagnosed HIV+. Validation sample consisted of 22,983 patients of whom 168 (0.73%) were HIV +	**Objective:** to evaluate a clinically relevant prediction tool to accurately categorize patients into risk groups for undiagnosed HIV infection: collected data on demographic characteristics, symptoms, history of STIs, sexual history, sexual practices, HIV testing history & other risk factors. **Outcome:** The risk scores accurately categorised patients into groups with increasing probabilities of infection
Federman et al 2012[55], Connecticut, USA	Prospective study	Electronic clinical reminder	All patients enrolled in the VA Connecticut healthcare system	Addition of a clinical reminder to the electronic medical record increased the amount of testing for HIV by 369%. 24 were diagnosed as HIV+	**Objective**: to assess effectiveness of an electronic clinical reminder added to medical records within the Veterans Affairs (VA) healthcare system (based on risk factors for HIV: Hepatitis, STDs, high risk sexual behaviour, alcohol or substance use disorders). **Outcome:** Testing led to the diagnosis of HIV in 24 patients over a 19-month period and were able to increase testing by 369%. The reminder was highly effective in those aged 64yrs or less but less evidence that it was effective for increasing HIV detection in those aged 65 or more.
Schrantz et al 2011 [56], Chicago, USA	Retrospective review of data from clinical and quality assurance records	HIV testing model using a web based patient tracker software	Patients in the Emergency Dept. (ED)	103,475 patients visited the ED (Jan 07-Nov 08) of which 1258 resulted in HIV testing and 54 were positive for HIV antibody. Among flagged patients, 39% had STIs, 11% had bacterial pneumonia. 262% increase in testing frequency	**Objective**: developed an Emergency Dept. HIV testing model using a web based patient tracking software (TRACKER) used for flagging selected patients for testing. Patient selection criteria included symptoms consistent with STIs, pregnancy, symptoms of bacterial pneumonia in <65yrs, IDUs and MSMs. **Outcome:** Strong association between the implementation of the system and a 262% increase in testing frequency (from 29.6 to 80.5 tests/month)
Menza et al 2009 [65], Washington State, USA	Data from medical records	Prediction/risk score model for HIV	Medical records data on MSM from an STD clinic	Of 1903 MSM tested more than once for HIV, 101 acquired HIV over 6.7yrs of follow up. Annual HIV incidence was 2.57%. During 4 yrs. follow up in control arm, of 2081, 144 acquired HIV with an incidence of 2.32%	**Objective:** to develop a prediction model for HIV acquisition in MSM (collected information on demographic variables, substance use, STD history, sexual behaviour & sexual partners)**. Outcome:** A new risk score was predictive of HIV acquisition in MSM
Goetz et al 2008 [57], 4 cities across USA	Prospective study	Clinical reminder intervention	Persons receiving healthcare at 5 veteran's	At the 2 intervention sites testing increased from 4.8% to	**Objective:** A multicomponent intervention (real time electronic clinical reminder that encourages HIV testing and feedback reports

Reference & Study location	Study Type and Intervention	Intervention /Comparison	Population targeted	No. or % with ICs, No. or % HIV+, HIV test rate	Main objective and outcome of study
			health administration facilities (2 intervention, 3 controls) between 2004 and 2006 who were at risk of HIV but had not been previously tested for HIV infection	10.8% and from 5.5% to 12.8%. 15 new HIV diagnoses were made in year pre-intervention vs 30 post intervention year.	and provider activation program). Clinical reminders were triggered by prior evidence of Hepatitis B or C infection, illicit drug use, STD (gonorrhoea, chlamydia, syphilis, or genital herpes & behavioural risk factors). **Outcome:** Use of clinical reminders increased the frequency of testing and number of new HIV diagnoses.
Sharghi et al 2005 [66], Cities across USA	A prospective cohort study	A clinical algorithm to predict early HIV-1 infection.	Study enrolled HIV-1 negative individuals at risk of HIV-1 infection. (4652 study participants)	86 individuals (13 women, 73 men) seroconverted during the study. The overall seroconversion rate was 1.3 per 100-person years	**Objective:** to look at association between self-reported clinical factors and recent HIV-1 seroconversion. Participants had to fill out a questionnaire at baseline. Study developed a clinical algorithm to predict early HIV-1 infection. HIV-1 seroconversion diagnosed using ELISA and confirmed by western blotting. **Outcome:** Four self-reported clinical factors were significantly associated with HIV-1 seroconversion in multivariable analyses: recent history of chlamydia infection or gonorrhoea, recent fever or night sweats, belief of recent HIV exposure and recent illness lasting >3 days. Two scoring systems, based on the presence of either 4 or 11 clinical factors were developed. Sensitivity ranged from 2.3% (with PPV of 12.5%) to 72.1% (with a PPV of 1%). Seroconversion rates were directly associated with the number of these clinical factors

IC: indicator condition, NIC: non-indicator condition, ED: Emergency Dept, STD: sexually transmitted disease, STIs: sexually transmitted infections, PPV: Positive predictive value, NPP: Negative predictive value, MSM: Men who have sex with men, ELISA: Enzyme linked immunosorbent assay, VA: veteran's affairs, CDSS: clinical decision support system, PCC: Primary care centre, HIDES: HIV indicator diseases across Europe study, CI: Confidence interval

Dosekun and colleagues assessed the impact of a targeted education programme for clinicians regarding late HIV diagnosis and awareness of HIV ICs with and without additional case note prompts for patients with ICs. They found that test offer was significantly higher when prompts were additionally used (34%) compared with education alone (3.1%) ($p<0.001$) [61]. However, Genotte et al (2013) also used education sessions to raise awareness of ICs and to assess whether HIV screening using rapid tests was feasible and acceptable (based on risk or presence of ICs) to a mainly African community. Although GPs felt more comfortable offering a test based on risk or presence of an IC, the study found that testing was usually not offered by the GPs due to time constraints [62].

Two studies used more targeted approaches to HIV testing using preselected ICs [24,63]. Elias and colleagues developed an HIV risk exposure and ICs questionnaire using 14 preselected ICs to support targeted screening. The study found that the self-completed questionnaire was feasible and accurately discriminated all non-HIV infected people without missing any HIV diagnoses in a low prevalence area [63]. In primary care settings in Spain, Menacho et al. prospectively compared IC guided testing using 4 preselected ICs (herpes zoster, seborrhoeic eczema, mononucleosis syndrome and leukopenia/ thrombocytopenia) with random testing using rapid finger stick tests. The study found using ICs was a feasible and less expensive way to improve diagnosis of HIV infection compared with a non-targeted approach [24].

We also identified a number of studies that developed risk prediction tools to identify individuals at risk of HIV infection based on HIV ICs and other risk factors [64-66]. HIV ICs used for these risk predictions tools mainly incorporated history of fever, STIs and STDs (included chlamydia, gonorrhoea and syphilis). Other behavioural risk factors incorporated in the tools included sexual behaviour/practices, number of sexual partners, PWID and substance use. These prediction models were successful in accurately categorising patients at increasing probabilities of infection [64,66] and risk scores were predictive of HIV acquisition in MSM [65].

4. DISCUSSION

Increasing HIV testing is crucial for identifying individuals who remain undiagnosed and linking them to care and treatment with ART. This is important for their own health and because treatment with ART substantially reduces risk of further transmission of the virus [67]. In the USA, the current guidance is for routine testing among all adults that come into contact with the healthcare system [11] but this is thought not to be best practice for the majority of European settings due to the poor cost-benefit ratio in certain areas where prevalence of HIV is low [68]. In the UK and Europe, HIV testing is recommended for individuals presenting with ICs associated with HIV infection [19,21]. The HIV in Europe initiative states that HIV testing of any person presenting with a condition associated with an undiagnosed HIV prevalence of >0.1% is cost-effective and promotes earlier diagnosis of HIV infection [21]. In the UK the 2008 BHIVA guidelines [10] were published with the aim of increasing HIV testing across healthcare settings to reduce the number of individuals with undiagnosed HIV infection. Routine testing in the UK is recommended in areas with > 2 per 1000 population prevalence based on cost effectiveness studies of HIV testing in the USA and France [69-71]. Regardless of local prevalence, testing should be offered to those presenting with any HIV ICs and/or other risk factors [10]. However, studies and reviews have shown there is a general lack of awareness and knowledge of the 2008 guidelines by HCPs [72-74]. Previous reviews and audits [75,76] show that adherence and application of these guidelines is poor, during the eight years after their publication, mainly due to limited test offer and lack of knowledge of HIV ICs by the HCP [75,77-79].

In this review, we have drawn together the most common HIV ICs and diseases that are most frequently seen in HIV infected individuals prior to or after receiving an HIV diagnosis. The most common ICs identified in those with PHI /AHI were fever/pyrexia of unknown origin [25-27,29,30], lymphadenopathy [25-28], headache [25-27,29], rash [25-27,29,30], weight loss [25,27-29], and gastrointestinal symptoms (nausea, vomiting, and diarrhoea) [25-29]. The strongest associations with HIV infection were seen for weight loss, vomiting, lymphadenopathy, fever and rash [28,30]. The most commonly reported STIs and BBVs in HIV infected individuals (either prior to or after diagnosis) were hepatitis C [22,23,33,34,44,47,54,80,81], hepatitis B [22,23,31,33,35,44,47,54], syphilis [31,33-37,80], chlamydia [34,35,45], gonorrhoea [33-35], condyloma acuminate [31,35,37],

cytomegalovirus [31,49] and genital herpes [33,35]. The strongest associations with HIV infection were seen for syphilis, gonorrhoea, hepatitis B/C and condyloma acuminata. The most common conditions associated with immunosuppression in individuals with HIV infection were pneumonia [17,20,31,35,37-46, 48-51,53,54,81-84], oral/oesophageal candidiasis [17,20,23,31,35,39,40,42,44,47,49-51,83], Kaposi sarcoma [31,39,42-46], lymphoma and non-Hodgkins lymphoma (NHL) [22,23,31,43], wasting syndrome [17, 20, 42] and cervical dysplasia/cervical cancer [17, 20, 22, 23, 35,45,47]. The conditions most strongly associated with immunosuppression were pneumonia, (incl, pneumocystis jiroveci pneumonia and bacterial pneumonia), oral candidiasis/candida oesophagitis, wasting syndrome and cytomegalovirus.

Interventions that incorporate HIV IC guided testing are especially warranted in areas of low HIV prevalence where HCPs are less familiar with HIV testing. Indeed, Chadwick et al. reported that a clinical decision support system (CDSS) prompt acted as a useful reminder for GPs to offer an HIV test in a low prevalence area (<0.5%) and was shown to have significant potential to increase HIV testing in such areas [85]. This review shows that HIV ICs have the potential to be used more effectively to guide HIV testing. Evidence from numerous studies have shown that had testing been offered to those presenting with an HIV IC, a high proportion of individuals between 21% and 37% [17,20] would have received a much earlier diagnosis. A study reviewing medical encounters before HIV diagnosis in the USA revealed that increased recognition of ICs for HIV testing prompted earlier HIV diagnosis in 22% of individuals [48]. Approximately 30% of newly diagnosed adults with HIV infection reported at least one IC before HIV diagnosis and that being tested for HIV within 6 months of being diagnosed with an IC reduced risk of late HIV presentation by 50% [33]. Results from the HIDES I and II studies [22,23] showed that patients with preselected indicator diseases had an HIV prevalence of >0.1%, providing firm evidence that IC guided testing provides a valuable opportunity to identify individuals with HIV infection.

In the UK, the National Institute for Health Care Excellence (NICE) have recently produced a draft quality standard document [9] (https://www.nice.org.uk/guidance/GID-QS10040/documents/draft-quality-standard) to encourage uptake of HIV testing which is due to be published in August 2017. It discusses interventions to improve the uptake of HIV testing among adults and young people that may have undiagnosed infection. This document has produced a list of HIV ICs which should be prioritised from the longer list identified by HIV in Europe Initiative. One of 6 questions open to consultation is 'We have identified indicator conditions that could be a priority for local measurement from the longer list of indicator conditions identified by HIV in Europe. Will it be practical to implement this?'. The list includes HIV ICs that service providers may wish to focus on as priorities, feedback from this document will be useful to aid any future interventions to improve uptake of HIV testing. Prioritising and focusing on HIV ICs that commonly present themselves could better inform testing strategies to identify HIV infected patients. Indeed, work is in progress to update guidelines for specialities other than HIV, such as dermatology or cancer, for the management of HIV ICs and AIDS defining conditions (ADCs), with a recent study showing that HIV testing was only recommended in 6 out of 17 guidelines for treating conditions that are also ADCs (35%) and 24 of 61 guidelines for treating conditions that are also HIV ICs (39%) [86].

The studies on common HIV ICs and diseases reviewed here provide information on using them as important indicators of potential underlying HIV infection, which could be used within prediction tools to flag that an HIV test should be offered, giving a more targeted approach to testing. Computer prompts avoid the HCP having to make a personal judgment on the risk of HIV and provides a platform for discussing having an HIV test, based on a prediction model ,which addresses some of the barriers to testing that are commonly reported by HCPs [74]. Interventions that have used ICs as a guide to testing (as well as other risk factors for HIV) alongside provider education sessions to improve awareness of HIV ICs are more effective in increasing HIV testing rates than education alone. Education and training of HCPs needs to continue and should focus on HIV ICs most likely to be encountered in primary care to help reduce incidence of late diagnosis. Strategies or interventions that empower or prompt GPs to test and enhance awareness of the national guidelines for IC HIV testing may help to find those with undiagnosed infection and reduce late diagnosis of HIV.

5. LIMITATIONS

This review is not a full review as it only includes grey literature from BHIVA conference proceedings (2010 to 2017) and articles included in the review are those that have encompassed the search term keywords outlined in the methods section (found within the article title, keywords or abstract). Therefore, some relevant articles may not be included. However, further articles were found by hand searching article reference lists. Comparing studies in this review should be interpreted with caution due to the different HIV testing guidelines, methodologies used to collect the data and possible differences in condition/disease prevalence between and within countries.

6. CONCLUSIONS AND RECOMMENDATIONS

This review provides a summary of important information for early detection strategies so that HIV infected individuals can receive a timely HIV test. Increased awareness of HIV infection within the primary care setting is paramount and could be improved by using computer prompts/reminders based on common HIV ICs to aid the HCP in appropriate offering of an HIV test. More targeted testing for HIV based on diagnosis of an HIV IC is an important strategy which has been shown to be effective and could potentially help reduce onward transmission and help control the HIV epidemic.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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