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CME/CE Article

Practice Tips

Rutgers François-Xavier Bagnoud Center
SCHOOL OF NURSING

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CE Continuing Education

Inflammation in Persons Living with HIV

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PROVIDER

Provided by the François-Xavier Bagnoud (FXB) Center, School of Nursing, Rutgers, The State University of New Jersey and the Center for Continuing and Outreach Education at Rutgers Biomedical and Health Sciences.

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STATEMENT OF NEED

There is a complex interaction between HIV infection, inflammation, and the immune system. Antiretroviral therapy (ART) has evolved to a point where most persons living with HIV (PLWH) can achieve an undetectable viral load within 12 weeks of starting treatment. However, chronic inflammatory processes still occur even in well-controlled HIV infection. Therefore, in an effort to further improve disease outcome, methods to decrease chronic inflammation have become a new focus of research.

This activity will review the most common comorbidities encountered in PLWH and discuss their relationship to environmental and genetic risk factors, HIV-related inflammatory state, and ART.

TARGET AUDIENCE

This activity is designed for physicians, physician assistants, advanced practice nurses, nurses, and other health care professionals in New Jersey who are involved in the care of people infected with HIV.

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Participants should read the learning objectives, review the activity in its entirety, and then complete the self-assessment test, which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or more on the self-assessment test, participants will receive a letter of credit 4 weeks after receipt of the self-assessment test, registration, and evaluation materials. This activity may also be completed online at http://ccoe.rbhs.rutgers.edu/catalog/.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be better able to:

1. Identify manifestations of inflammation in PLWH.
2. Articulate benefits of early and continuous undetectable HIV viral load to decrease chronic inflammation.
3. Recognize risk factors for common comorbidities in PLWH.
4. Identify approaches to prevent and manage comorbidities and co-infection in order to control chronic inflammation.

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New Jersey HIVLinks Summer 2016
HIV, STD, and TB news and information for health professionals

Inflammation in Persons Living with HIV

Jihad Slim, MD, and Christopher F. Saling, MD

LEARNING OBJECTIVES:

By the end of this activity participants should be better able to:

1. Identify manifestations of inflammation in PLWH
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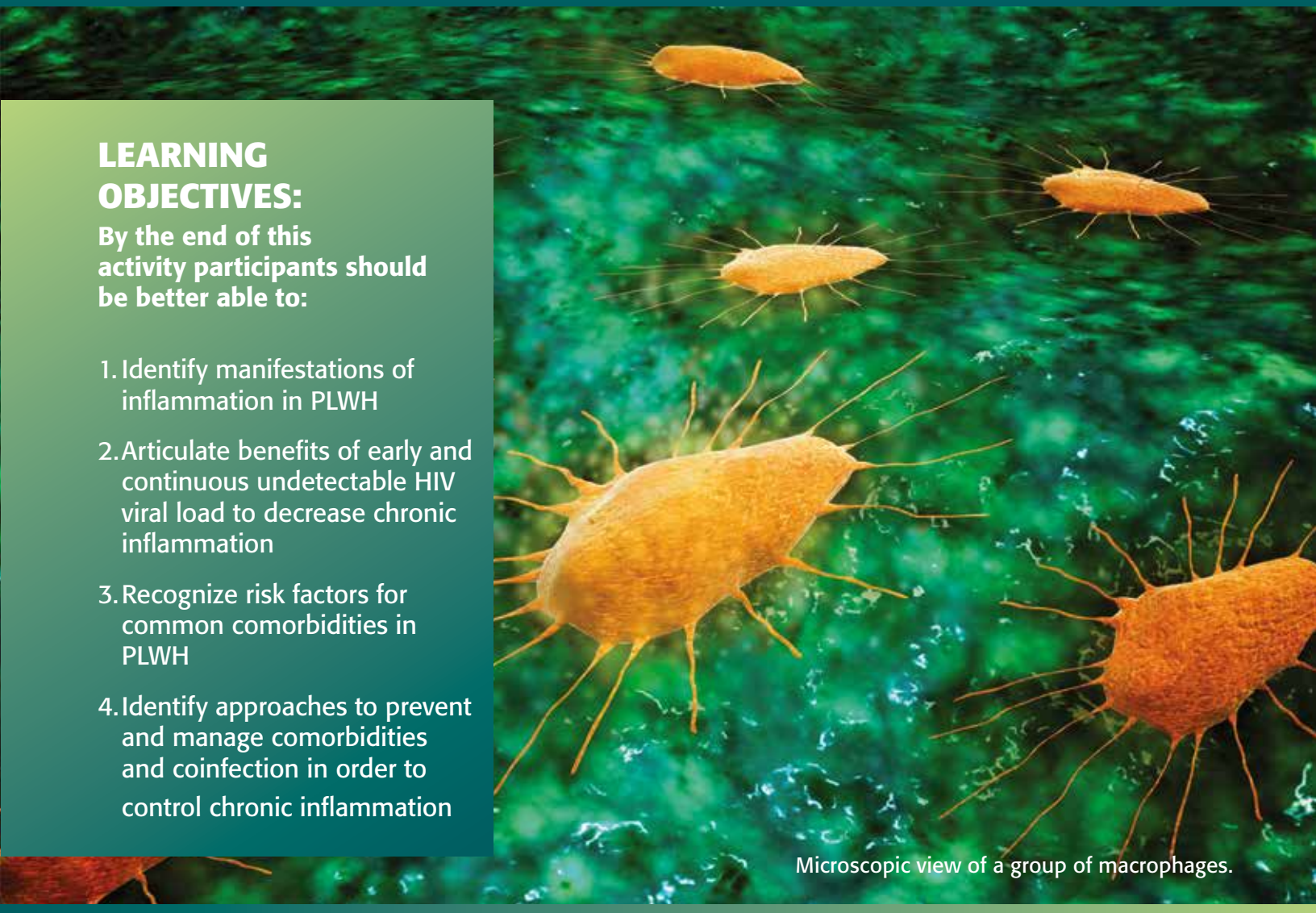
4. Identify approaches to prevent and manage comorbidities and coinfection in order to control chronic inflammation



Microscopic view of a group of macrophages.

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NJ Health New Jersey Department of Health

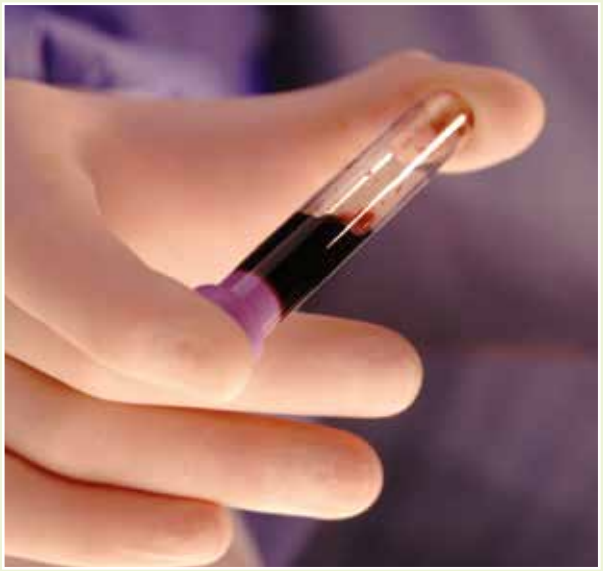
Rutgers François-Xavier Bagnoud Center SCHOOL OF NURSING

Inflammation in Persons Living with HIV

INTRODUCTION

There is a complex interaction between HIV infection, inflammation, and the immune system. Antiretroviral therapy (ART) has evolved to a point where most persons living with HIV (PLWH) can achieve an undetectable viral load within 12 weeks of starting treatment. However, chronic inflammatory processes still occur even in well-controlled HIV infection. Therefore, in an effort to further improve disease outcome, methods to decrease chronic inflammation have become a new focus of research.

Inflammatory markers appear to directly correlate with morbidity and mortality in PLWH. This connection has been studied most in those with cardiovascular complications, but also fits well in other models of comorbid conditions that inflict PLWH. Some of these comorbidities include diabetes mellitus (DM), non-AIDS related cancers, HIV-associated neurocognitive disorders, osteoporosis, liver fibrosis, and renal insufficiency. For the sake of completeness, when studying any of those conditions in PLWH, one must take into consideration a variety of factors. These include: **(1)** the degree that HIV infection is currently controlled, **(2)** the duration that HIV has been controlled, **(3)** the extent of immune damage prior to the initiation of ART, **(4)** the amount of immune system recovery with ART, **(5)** the presence of other co-infections, **(6)** the role of environmental factors, and **(7)** the effect of ART on the co-morbidity itself.



Over the past two decades, ART has dramatically reduced the incidence of morbidity and mortality related to both HIV and opportunistic infections. However, even with this advancement in HIV treatment, the life expectancy of an HIV-infected individual is still slightly less than that of the general population. The highest estimated life expectancy for a newly diagnosed HIV-infected 20 year old on ART in the United States (US) or Canada is just above 70 years[1]; and, inflammation is theorized to be the driving factor for this gap.

The new challenges facing PLWH are non-AIDS related conditions. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) prospective HIV cohort study found that the most common comorbidities leading to death in PLWH were non-AIDS cancers, cardiovascular disease (CVD), and liver disease.[2] Morlat et al. expressed these same findings in a study in France in 2010.[3] The Swiss HIV cohort study by Hasse et al. revealed that stroke, myocardial infarction, DM, fragility bone fractures, and non-AIDS-defining malignancies were significantly elevated for persons aged ≥65 years.[4] Guaraldi et al. performed a case-control study in ART-experienced patients treated at Modena University, Italy, from 2002 through 2009. They were compared with age-, sex-, and race-matched adults from the general population. They specifically looked at noninfectious comorbidities (NICMs), which included CVD, hypertension, DM, bone fractures, and renal failure. The study defined polypathology (Pp) as the concurrent presence of ≥2 NICMs and concluded that the prevalence of Pp among PLWH aged 41-50 years was similar to that among controls aged 51-60 years. Logistic regression models showed that independent predictors of Pp in the overall cohort were age (odds ratio [OR], 1.11), male sex (OR, 1.77), nadir $CD4^+$ count <200 cells/μL (OR, 4.46), and ART exposure (OR, 1.01).[5]

The pivotal SMART trial provided evidence of the association of inflammatory biomarkers and coagulation with increased risk of all-cause mortality.[6] They also showed that interleukin-6 (IL-6) and D-dimer were significantly associated with increased risk of CVD and other causes of death, even in patients on ART.[7] Tenorio et al. conducted a case-control study that concurred with these findings, concluding that soluble inflammatory markers correlated with non-AIDS defining events in PLWH virally suppressed on therapy.[8]

This paper will review the most common comorbidities encountered in PLWH and discuss their relationship to environmental and genetic risk factors, HIV-related inflammatory state, and ART. Since the inflammatory component, which is a correlate of T-cell activation, is much more pronounced when the virus is not suppressed, we will limit the discussion towards PLWH receiving effective treatment for HIV.[9]

Although successful ART does not suppress all inflammatory mechanisms associated with HIV, it has been shown to decrease some immune activation markers to the level of HIV-uninfected individuals, particularly monocyte-macrophage activation.[10]

It is relatively well established that a chronic inflammatory state in PLWH receiving appropriate ART is primarily related to the extent of damaged gut-associated lymphoid tissue and its subsequent microbial translocation, as well as the presence of other active viral infections like cytomegalovirus (CMV) and hepatitis C virus (HCV).[11,12] Furthermore, in clinical practice HIV viral load (VL) is measured intermittently and there are different cut offs for detection. Thus, it is conceivable that low-grade or intermittent viremia is actually occurring in PLWH that are classified as undetectable. This phenomenon could also play a role in persistent inflammation.

PATHOPHYSIOLOGY OF INFLAMMATION IN PLWH

Acute HIV infection is associated with immune activation and severe inflammatory reaction, as evidenced by the intense surge of cytokines such as interferon-α, interferon-Ɣ, tumor necrosis factor, and IL-6.[13] There is a profound depletion of $CD4^+$ cells from the gut during acute infection, which only partially improves with effective ART.[14,15] This explains the reasoning behind intestinal microbial translocation and subsequent immune activation.[16]

One method for studying microbial translocation is through the measurement of serum lipopolysaccharide (LPS). The Strategies for Management of Anti-Retroviral Therapy (SMART) study revealed that soluble CD14, a marker of monocyte response to LPS, was an independent predictor of mortality in PLWH.[17] This was corroborated by another case-control study by Hunt et al., which concluded that gut epithelial barrier dysfunction independently predicts mortality in individuals with virally suppressed HIV infection who also have a history of AIDS.[18] Microbial translocation is currently one of the most accepted elements defining the pathophysiology of a chronic inflammatory state present in PLWH on ART with well-controlled viremia.

Another important determinant of this inflammation is co-infection. Modjarrad et al. reviewed the literature up to April 2010 and found that treatment of *Mycobacterium tuberculosis*, syphilis, and other infections significantly decreased HIV VL, even when no ART was used.[19] In another prospective study using CMV polymerase chain reaction (PCR), Deayton et al. established a direct correlation of positive PCR findings with new AIDS-defining disorders and mortality in PLWH in the highly active ART era.[20] Furthermore, in review of CMV in PLWH, Barrett et al. summarize the evidence that CMV could be an important cofactor in the development of age-related morbidities in PLWH.[21]

Since HCV is another prevalent virus found in 20-25% of PLWH, it is relevant to study its impact on immune recovery after HIV is effectively suppressed. Zaegel-Faucher et al. retrospectively reviewed this data in patients with undetectable HIV VL for at least 3 years and concluded that $CD4^+$ percentage and CD4/CD8 ratio were lower in patients co-infected with HCV compared to those with mono-infection, despite having similar ART regimens and $CD4^+$ and $CD8^+$ counts at first undetectable HIV VL.[22]

The association between co-infection and chronic inflammation in PLWH was further established by Masia et al., who prospectively studied multiple blood biomarkers of inflammation in mono-infected PLWH compared to those co-infected with human herpesvirus-8 (HHV-8).[23] Both groups had a suppressed HIV VL, but inflammation and immune activation were significantly higher in those with HHV-8 co-infection.[23] This further highlights that co-infection is a key component of the residual immune dysregulation present in PLWH receiving suppressive ART.

A third factor relating to inflammation in PLWH is T-cell function. It is unclear if immune dysregulation leads to inflammation or vice versa. Nonetheless, they are usually present together and both contribute to the burden of comorbid illnesses.[24] Hunter et al. studied the relationship of immune activation and increased $CD4^+$ count when HIV was suppressed with ART and found that increased T-cell activation was associated with shorter duration of viral suppression, HCV co-infection, frequent low-level viremia, lower nadir $CD4^+$ T-cell counts, and a lower gain in $CD4^+$ T-cells.[25] In an elegant study of impaired gut junctional complexes by Tincati et al., a relationship was established between gut damage, HIV viral reservoir, and $CD4^+$ response to ART.[26] These researchers concluded that the more damage to the gut and the larger the reservoir, the less of an increase in $CD4^+$ cells while on suppressive ART.[26]

It has been well established that a high proportion of PLWH who delay ART until the $CD4^+$ count drops below 200 cells/mm^3 do not achieve a normal $CD4^+$ count, even after a decade of effective therapy.[27] Engsig et al. shed more light on this concept by examining data on PLWH whose VL was suppressed on ART for >three years with a $CD4^+$ count <200 cells/mm^3.[28] They were able to identify that increasing age, lower initial $CD4^+$ count, and injection drug use were among the risk factors contributing towards a continued low $CD4^+$ count, as well as clearly show a higher all-cause mortality in this subgroup compared to those who achieved a $CD4^+$>200 cells/mm^3 after three years of suppressive therapy.[28] Furthermore, in a prospective, observational cohort study in persons with acute or early HIV infection, Le et al. concluded that early suppressive therapy led to better immune recovery.[29] Additionally, INSIGHT START study group found that patients with $CD4^+$ >500 cells/mm^3 benefit from ART when started early compared to patients who waited until $CD4^+$ reached 350 to initiate ART.[30] Those who started treatment when

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CD4+>500 had significantly less morbidity and mortality.[30] Negredo et al. in a cross-sectional, case-control study established that CD4+ nadir was the best predictor of a discordant immune response (defined as CD4+<350 after >2 years of VL<50 copies/ml) and also suggested early initiation of ART.[31] Lastly, in the ICONA study, Lapadula et al. were able to define immune non-responders as <120% increase in CD4+ cell count by the time VL is undetectable.[32] This subgroup of PLWH had higher risk of severe clinical events than immune responders.[32]

Finally, ART must always be considered a potential cause of adverse events, and therefore, a possible contributor towards inflammation and aging in those with controlled HIV infection.[33] Leeansyah et al. studied telomerase activity and length in vitro by looking at peripheral blood mononuclear cells (PBMCs) from PLWH receiving a nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen, and found that they had significantly lower telomerase activity than both HIV-uninfected persons and PLWH receiving a non-NRTI-containing regimen.[34] Telomerase length was inversely associated with age, as well as the total duration of NRTI-containing therapy.[34] This study concluded that NRTIs at therapeutic concentrations, specifically tenofovir, inhibit telomerase activity and leads to its accelerated shortening in activated PBMCs, which could play a role in the enhanced aging of PLWH.[34]

In summary, indicators of poor prognosis in PLWH are increased markers of inflammation and immune activation. These often correlate with low current and/or nadir CD4+ T-cell counts, co-infections, and gut immune damage with microbial translocation.[35,36] What makes this subject so difficult to study are the diversity of the comorbidities involved and the variability of the markers that seem to be important to measure.[37] However, it is probably safe to assume that the better the immune system, the less the degree of chronic inflammation, and, thus, the closer the incidence of comorbidities and life expectancy of a PLWH with undetectable VL to that of the general population.[37,38]

CARDIOVASCULAR DISORDER

Multiple studies have identified HIV as an independent risk factor for acute myocardial infarction (AMI). Freiberg et al. reviewed data from participants in the Veterans Aging Cohort Study that included both HIV-infected and HIV-uninfected individuals. This study concluded that infection with HIV was associated with a 50% increased risk of AMI beyond which was explained by recognized risk factors.[39] In two cohorts from the Partners HealthCare System in Boston, Triant et al. compared the rate of AMI in HIV-infected and HIV-uninfected patients while adjusting for age, gender, race, hypertension, DM, and dyslipidemia. They, too, concluded that there was an increased risk of AMI in PLWH, especially in women.[40]

When attempting to analyze the reasoning for the higher risk of AMI in PLWH, three factors are confronted:

Inflammation or dysregulation of the immune system; this is related to HIV viremia, low CD4+ cell count (nadir or current), microbial translocation, and co-infections.[41-46]

Traditional risk factors for CVD; especially smoking, DM, and dyslipidemia.[47-50] These risk factors are more prevalent in PLWH then in the general population.[47-50] Also, obesity prevalence is increasing in PLWH, and as the HIV population ages, the prevalence of hypertension within this group will increase as well.[47-50]

ART; namely abacavir and certain protease inhibitors such as ritonavir + lopinavir.[51,52]

There exist interactions between HIV infection and these risk factors for AMI. Valiathan et al. compared HIV-infected smokers and non-smokers that had documented viral suppression on ART to HIV-uninfected smokers and non-smokers.[53] They found that smoking and HIV infection both independently influence T-cell immune activation and function, and together they present the worst immune profile.[53] Another example that highlights this interaction between HIV and AMI risk factors is the use of ritonavir + lopinavir and a higher incidence of hyperlipidemia and potential insulin resistance.[54] Lastly, Okeke et al. reviewed the hospital discharge data from the Nationwide Inpatient Sample from 2002 to 2012 looking specifically for patients with AMI or stroke.[55] They used multivariable logistic regression to evaluate the association between HIV and in-hospital death.[55] They found that patients with a history of AIDS were significantly more likely to die in-hospital after AMI and stroke than HIV-uninfected patients.[55] This disparity was not observed when PLWH without a history of AIDS were compared to HIV-uninfected patients.[55]

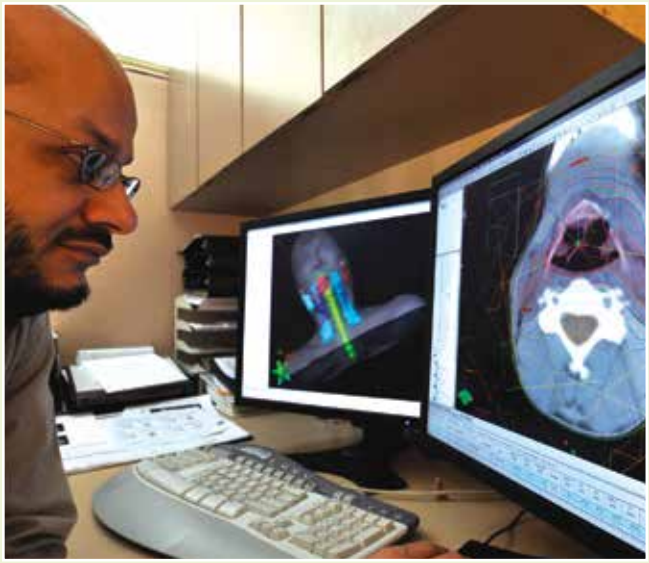
Based off the above findings, the best chances of reducing the risk of PLWH for CVD include the following: completely suppressing the HIV VL as early as possible with an ART regimen that has not been implicated in increasing CVD risk factors; advising patients to stop smoking and increase their physical activity; and controlling any dyslipidemia, hyperglycemia, or hypertension.[56]

DIABETES MELLITUS

The incidence of DM may be increased in PLWH.[4] The pathophysiology can be divided into the same 3 features:

Inflammation and HIV lipodystrophy; this involves adipose tissue redistribution, mitochondrial dysfunction, altered differentiation of adipocytes, and increased adipocyte lipolysis.[48,57] This leads to altered adipokine secretion, as well as the release of pro-inflammatory cytokines and free fatty acids.[48,57] This, in turn, exacerbates chronic inflammation, dyslipidemia and insulin resistance.[48,57]

Traditional risk factors; some DM risk factors are becoming more prevalent in PLWH, namely aging and obesity.[50] Family history is also an important risk factor. Finally, co-infection with HCV plays a significant role in the risk of DM in PLWH, and its prevalence depends on the same risk factors for the acquisition of HIV[58,59]; it is estimated that 25% of PLWH in the US are co-infected with HCV.[58,59]



Specific ART regimens as a risk factor for DM; the D:A:D study implicated zidovudine and stavudine as two NRTIs that are significantly associated with a higher incidence of DM, even after adjustment for risk factors for DM and lipids.[60]

An illustration of the interaction of these risk factors can be found in the paper by Betene et al.,[61] whereby they assessed inflammatory markers in a cohort of 3,695 PLWH with an average CD4$^+$count of 523 cells/mm^3.[61] These patients did not have DM and were on ART. 137 patients developed DM over an average follow up period of 4.6 years. The median levels of IL-6 and hs-CRP were significantly higher among those who had developed DM compared with those who did not.[61] Body mass index, age, co-infection with hepatitis B or C, and smoking status were all associated with an increased risk of DM.

NON-AIDS RELATED MALIGNANCIES

Malignancies that are considered AIDS-related such as Kaposi's sarcoma, primary central nervous system (CNS) lymphoma, and cervical cancer have dramatically declined since the advent of suppressive ART.[62] Furthermore, the incidence of non-AIDS related malignancies (NARM) including anal cancer, hepatocellular carcinoma, head and neck cancers, lung cancers, non-Hodgkin's lymphoma, and melanoma have increased so significantly that they now represent one of the most common causes of death in PLWH in the US.[37] Risk factors are multiple and can be divided into the 3 previously mentioned categories[63]:

Immune dysregulation and chronic inflammation; these processes can promote increased cell proliferation and generate potentially damaging reactive oxygen species.[64] The immune dysfunction associated with HIV infection may also lead to impaired immune surveillance with an impaired ability to both detect and eliminate early tumor cells.[65] Powles et al. reported from their large prospective cohort that a nadir CD4+ count <200 cells/μL had a significant association with NARM.[66]

Traditional risk factors for NARM; some are more prevalent in PLWH such as smoking, with its subsequent increase in lung cancer, as well as hepatitis B and C viruses, with their associated risk for hepatocellular carcinoma.[67,68] Hodgkin's lymphoma in PLWH is seen at a higher incidence than that of the general population and is often associated with EBV co-infection.[69] Probably the highest increase in cancer types in PLWH compared to those that are HIV-uninfected are related to HPV.[70] Associated cancer types to this co-infection include anal cancer, head and neck cancer, and cervical cancer (which is an AIDS-related malignancy).[70]

ART regimens that increase NARM incidence, most-notably hepatocellular carcinoma (HCC); Ryom et al. reviewed the association of antiretroviral drugs and their association with HCC from a large D:A:D cohort.[71] In this study, the cumulative use of stavudine, didanosine, tenofovir disoproxil fumarate (TDF), and amprenavir were independently associated with increased end stage liver disease and HCC rates.[71] Conversely, cumulative exposure to emtricitabine, and nevirapine were actually shown to be protective against HCC.[71]

An example of the interaction between these risk factors towards NARM is HCV predisposing an individual to DM, which in itself is an independent risk factor for HCC.[72]

RENAL DISEASE

HIV infection is a well-established risk factor for chronic kidney disease (CKD) and subsequent end stage kidney disease (ESKD) in the US.[73] The risk factors can be divided as were the previous co-morbidities:

Immune dysregulation and chronic inflammation; HIV-associated nephropathy (HIVAN) is most commonly seen in

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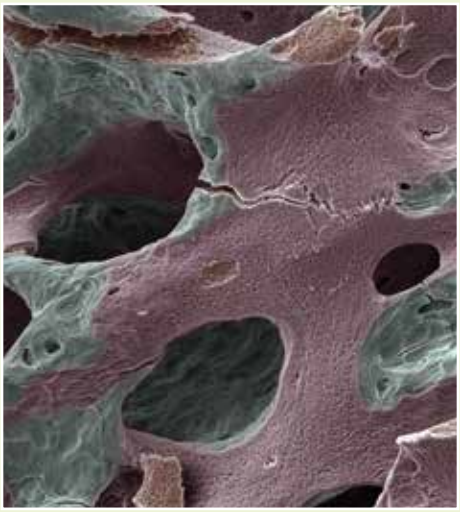
pictured right: Osteoporotic bone, SEM



those of African descent in the setting of untreated HIV infection with advanced immunosuppression.[75] It is characterized clinically by heavy proteinuria without hematuria on urinalysis, as well as rapid glomerular filtration rate (GFR) decline to ESKD within a few months.[74] Nonetheless, the chronic inflammatory state that persists after viral control may play a role in CKD, but it seems minimal at this point.[75]

Traditional risk factors for ESKD; DM, HTN, HCV co-infection, African American race, and aging seem to play the major role for predicting ESKD once HIV is well controlled.[75] Also, the use of potentially nephrotoxic agents like NSAIDs, diuretics, and ACE inhibitors contribute towards renal disease in PLWH.[76]

ART causing renal disease; nephrotoxicity has been mainly linked to TDF, which can cause several patterns of kidney injury. The most common of these injury forms is proximal tubular dysfunction, but TDF, although rarely, may lead to acute kidney injury, CKD, and nephrogenic diabetes insipidus.[77]

Again, here is an example to show the various interactions involved between the risk factors of a specific comorbidity, in this case renal disease, and HIV. HCV is a co-infection that increases the chronic inflammatory state present in PLWH, which could then increase the incidence of DM, and, subsequently, both cofactors could contribute towards renal damage.[78]

LIVER FIBROSIS

The effect of HIV on liver disease was well characterized by Towner et al. in a case-control study which concluded that HIV-infected individuals have a higher risk of hepatic dysfunction and hepatic-related death compared to those without HIV infection, even with adjustment for known hepatic risk factors.[79]

Co-morbidities contributing towards liver disease and fibrosis can be divided into the same three categories:

Immune dysregulation and chronic inflammation; Marchetti et al. revealed that HIV co-infected patients (mainly HCV) with higher Tumor necrosis factor alpha (TNF-α) plasma levels had a 13-fold increase in the risk of progression to a fibrosis-4 (Fib-4) >1.45.[80] However, these patients were not receiving ART.[80] A more recent study suggests that ART with good immune reconstitution can slow down liver fibrosis in HIV/HCV co-infected patients.[81]

Traditional risk factors for liver fibrosis; alcohol abuse, steatosis, rare genetic diseases (Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency), drug-induced liver injury, or co-infection with HCV or HBV can all lead to liver injury and, ultimately, liver fibrosis.[81]

ART causing liver disease; most ART can cause drug induced liver injury and this side effect is more commonly reported in patients with underlying chronic liver disease.[82] Although this could lead to permanent liver failure, most of these hepatotoxic side effects resolve after removal of the offending agent.[82,83] A different mechanism of liver injury that is associated with progressive fibrosis has been linked to ART when lipodystrophy occurs with subsequent nonalcoholic steatohepatitis.[83]

BONE DISEASE

The prevalence of osteoporosis, as well as fractures, in HIV-infected individuals is more than three times greater when compared with HIV-uninfected controls.[84,85]

Reasons for decreased bone mineral density (BMD) in PLWH can be split into the following mechanisms:

Immune dysregulation and chronic inflammation; Yong et al. studied risk factors of fragility fractures in a matched case control study in patients with HIV and found that a low $CD4^+$ cell count, use of corticosteroids, and anti-epileptic medications were strong predictors for fragility fractures.[86] Furthermore, multiple studies have linked chronic inflammation with low BMD.[87]

Traditional risk factors for decreased BMD; low Vitamin D, tobacco smoking, excessive alcohol use, and increased use of selective serotonin re-uptake inhibitor (SSRI) have all been associated with low BMD.[88,89] These risk factors for osteoporosis are more prevalent in PLWH.[89]

ART causing bone disease; TDF is the antiretroviral agent with the most potent decrease in BMD, especially at the start of therapy.[90] Efavirenz has also been linked to bone disease because it has been shown to decrease vitamin D levels.[90]

HIV ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND)

HAND is inclusive of a range of neurocognitive disorders related to HIV from asymptomatic cognitive disability to HIV dementia, an AIDS-defining diagnosis that was commonly encountered prior to the advent of effective ART.[91] This complex neurocognitive disorder is probably the result of multiple factors, including inflammation with possible atherosclerotic consequences, as well as concomitant abuse of drugs, aging, and potential neurotoxicity of ART drugs.[92]

Potential mechanisms driving HAND in PLWH will be described within the same three categories:

Immune dysregulation and chronic inflammation; systemic and CNS inflammation seem to play a central role in the pathophysiology of HAND.[93]

Traditional risk factors for HAND; aging, atherosclerosis, thrombosis, mental illness (depression, anxiety, post-traumatic stress disorder, psychosis, etc.), HCV, and drug use are all linked to HAND and are all more prevalent in PLWH.[94]

ART causing neurocognitive disorder; when analyzing the effect of ART on neurologic function, it is essential to differentiate separate drug toxicity (i.e., efavirenz) from lack of CNS drug penetration which could potentially cause persistent HIV related CNS damage.[95]

An obvious interaction between these factors would be chronic inflammation from HIV infection, leading to atherosclerosis with subsequent strokes and ischemic damage, which, in turn, would cause neurologic disease.[96]

HOW TO COMBAT CHRONIC INFLAMMATION IN PLWH

Many investigators have studied different interventions to decrease the inflammatory response in PLWH.[97-107] These interventions can be divided into two groups. The first is using different antiretroviral agents, while the second is using other alternative methods in order to manipulate immune dysregulation and alleviate chronic inflammation.[97-107]

Group 1: ART Intervention

This group can further be divided into three subcategories based on differing treatment methodology:

1. The first method calls for adding another antiretroviral agent to an already suppressive regimen in an effort to decrease inflammation.[97] This approach has generally been unsuccessful.[97]

2. The second approach is switching patients who are virologically controlled to a different ART regimen while measuring markers of inflammation.[98-100] The SPIRAL trial used this method in patients who had undetectable HIV VL on a boosted Protease inhibitor (PI) and then randomly switched them in a 1:1 fashion to Raltegravir (RAL).[98] At 48 weeks after the randomized switching from a boosted PI to RAL, results showed significant changes in several cardiovascular biomarkers that could not be completely explained by lipid changes alone.[98] Other RAL switch studies from both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and enfuvirtide (an HIV fusion inhibitor) that measured inflammatory biomarkers also favored the RAL switch arm.[99,100] It is worth noting, however, that none of these studies had a clinical endpoint.[98-100]

3. A third method aimed to discover ideal antiretroviral treatments for suppressing chronic inflammation in PLWH is a head-to head trial of different ART regimens in patients that are naïve to treatment. Hileman et al. examined markers of inflammation and monocyte activation in a randomized controlled blinded study of single tablet regimen of cobicistat/elvitegravir/emtricitabine/TDF versus efavirenz/emtricitabine/TDF.[101] They concluded that the elvitegravir-containing regimen had a greater decrease in sCD14, hs-CRP, and Lp-PLA2 levels compared to the efavirenz-containing regimen.[101]

Group 2: Non-Antiretroviral Intervention

There have been a variety of promising studies suggesting alternate therapies to treat chronic inflammation. Multiple published trials revealed that rosuvastatin showed benefit in reducing inflammation markers and immune activation.[102-104] Wooten at al. examined the effect of healthy diet and exercise on inflammation in PLWH with undetectable VL and dyslipidemia.[105] In this study, these interventions effectively reduced plasma Lp-PLA2 mass.[105] Villar-Garcia et al. conducted a double-blind, randomized, placebo-controlled trial of *Saccharomyces boulardii* in 44 patients with viral loads of <20 copies/ml for at least 2 years. These researchers found that this fungus was very effective at decreasing microbial translocation and inflammation parameters.[106] Another innovative approach at non-ART intervention was a 12-week, single-arm, open-label study, whereby Sereti et al. tested the efficacy of IL-7 adjunctive therapy on T-cell reconstitution in peripheral blood and gut mucosa in 23 ART suppressed PLWH with incomplete $CD4^+$ recovery. They observed that administration of r-hIL-7 improved the gut mucosal abnormalities of chronic HIV infection, as well as attenuated the systemic inflammatory and coagulation abnormalities associated with said gut disease.[107] Although promising, these non-ART interventions are still investigational.

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CONCLUSION

A practical clinical approach to the management of PLWH should take into account the following:

1. Early ART with complete suppression of HIV VL[108] has been shown to best minimize the degree of chronic inflammation, immune activation, and microbial translocation by maintaining a functional immune system, while at the same time, limiting the amount of immune dysregulation.
2. The prevention and treatment of co-infection is critical for the control of chronic inflammatory processes in PLWH. Counseling about the importance of continued condom use, following vaccination protocols for HPV, HAV, HBV, influenza, and pneumococcus, providing appropriate cancer screening, and treating HCV and HBV would significantly decrease immune activation in this patient population.
3. We must always be wary of the adverse effects of certain antiretroviral regimens and continue to explore the use of newer and potentially less toxic agents that may better suppress chronic inflammation by not contributing towards other co-morbidities. Furthermore, non-ART interventions such as proper diet and exercise should be emphasized as part of our armamentarium against immune dysregulation.

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CE Continuing Education

Inflammation in Persons Living with HIV

POST TEST — Page 1 of 1

Questions refer to article content. To receive CME/CNE/CEU credit, complete the post test, registration and evaluation forms on-line at *http://ccoe.rbhs.rutgers.edu/catalog/* or fill in the forms below and on the following pages and mail or fax to CCOE at the address on the registration form.

1. Which of the following co-morbidities are the most common causes of death in PLWH on a suppressive ART regimen?
   a. Renal failure, Kaposi's sarcoma, and Pneumonia
   b. Non-AIDS defining cancers, cardiovascular disorders, and liver cirrhosis
   c. Pulmonary hypertension, congestive heart failure, and cachexia
   d. Stroke, lung cancer, and aging

2. Which one of the following is least likely to be associated with the chronic inflammatory state described in PLWH?
   a. High level of IL-6, CRP, and D-dimer
   b. Microbial translocation and high serum level of lipopolysaccharide (LPS)
   c. HCV, CMV, or TB co-infection
   d. High CD4 count and a suppressive ART regimen

3. Chronic inflammation in PLWH has been linked to the acceleration of the aging process. Which of the following does not contribute to this state?
   a. Low CD4 nadir
   b. Short telomerase
   c. Early treatment of acute HIV infection
   d. Microbial translocation.

4. CVD is more common in PLWH than in the general population. Which of the following is not a risk factor for CVD?
   a. Low CD4 nadir, smoking, and hypertension
   b. DM, obesity, and hyperlipidemia
   c. Abacavir and lopinavir/ritonavir
   d. Raltegravir and tenofovir disoproxil fumarate /emtricitabine

5. DM is more common in PLWH than in the general population. Which of the following does not contribute towards this increased incidence?
   a. Use of integrase inhibitors
   b. Increase in obesity
   c. Cumulative use of zidovudine
   d. Chronic active HCV

6. True or False: Hodgkin's lymphoma is seen at a higher incidence in PLWH than that of the general population.
   a. False
   b. True

7. The D:A:D cohort found that all of the following antiretroviral agents were associated with higher HCC rates except:
   a. Didanosine
   b. Nevirapine
   c. Amprenavir
   d. TDF

8. Which factor does not contribute towards renal toxicity in PLWH?
   a. Uncontrolled HTN
   b. Use of NSAIDs
   c. Cumulative use of raltegravir
   d. HCV co-infection

9. Which one of the following is not a risk factor for fragility fracture in PLWH?
   a. Vitamin E deficiency
   b. Low CD4 count
   c. Corticosteroids use
   d. Anti-epileptic medications such as phenytoin

10. Which of the following is the best intervention to decrease chronic inflammation in PLWH?
    a. Adding another antiretroviral agent to a regimen that has already suppressed VL
    b. Switching a protease inhibitor for an NNRTI
    c. Stop smoking and increase physical activity
    d. Use of IL-2 to boost the immune system

Inflammation in Persons Living with HIV

REGISTRATION FORM

CE Continuing Education

RUTGERS

In order to obtain continuing education credit, participants are required to:

(1) Read the learning objectives, review the activity, and complete the post-test.

(2) Complete this registration form and the activity evaluation form on the next page. Record your test answers below.

(3) Send the registration and evaluation forms to: Rutgers Center for Continuing & Outreach Education
▪ VIA MAIL: 30 Bergen St., ADMC 7, Newark, NJ 07103 ▪ VIA FAX: (973) 972-7128

(4) Retain a copy of your test answers. Your answer sheet will be graded and if you achieve a passing score of 70% or more, a credit letter will be mailed to you within four (4) weeks. Individuals who fail to attain a passing score will be notified and offered the opportunity to complete the activity again.

Online option: This activity will be posted at *http://ccoe.rbhs.rutgers.edu/catalog/* where you may obtain a credit letter upon successful completion of the online post-test and evaluation. ***Please note: CE credit letters will only be issued upon receipt of completed evaluation form.***

SELF-ASSESSMENT TEST *Circle the best answer for each question.*	**1.** A B C D	**2.** A B C D	**3.** A B C D	**4.** A B C D	**5.** A B C D
	6. A B	**7.** A B C D	**8.** A B C D	**9.** A B C D	**10.** A B C D

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Indicate the type of continuing education credit you wish to obtain as a result of your participation in this activity.

☐ **Nurses:** 0.98 CNE Contact Hour. Contact Hours Claimed: _____

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I attest that I have completed this activity as designed. I will report the number of credits/contact hours claimed during my filing of continuing education credit with professional organizations, licensing boards, or other agencies.

Signature Date

Release date: June 1, 2016 ▪ Expiration date: Credit for this activity will be provided through May 31, 2018.
A CE credit letter will be mailed to you in approximately 4 weeks.

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CE Continuing Education

Inflammation in Persons Living with HIV

EVALUATION FORM

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The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants.

Please note: CE credit letters will only be issued upon receipt of completed evaluation form.

PROGRAM OBJECTIVES: Having completed this activity, you are better able to:	Strongly Agree				Strongly Disagree
Objective 1: Identify manifestations of inflammation in PLWH	5	4	3	2	1
Objective 2: Articulate benefits of early and continuous undetectable HIV viral load to decrease chronic inflammation	5	4	3	2	1
Objective 3: Recognize risk factors for common comorbidities in PLWH	5	4	3	2	1
Objective 4: Identify approaches to prevent and manage comorbidities and coinfection in order to control chronic inflammation	5	4	3	2	1

OVERALL EVALUATION: This activity:	Strongly Agree				Strongly Disagree
Increased my understanding of the subject	5	4	3	2	1
Will influence how I do my job	5	4	3	2	1
Will help me improve my performance	5	4	3	2	1
Will help me collaborate with other healthcare professionals	5	4	3	2	1
Was evidence based and scientifically balanced	5	4	3	2	1
Was free of commercial bias or influence	5	4	3	2	1
Met my expectations	5	4	3	2	1

Based on the content of the activity, what will you do differently in the care of your patients and/or regarding your professional responsibilities?

☐ Implement a change in my practice/workplace

☐ Seek additional information on this topic

☐ Do nothing differently; current practice/job responsibilities reflects activity recommendations

☐ Do nothing differently; Content was not convincing

☐ Do nothing differently; System barriers prevent change

If you anticipate changing one or more aspects of your practice and/or professional responsibilities please briefly describe how you plan to do so.

_____

_____

If you plan to change your practice and/or professional responsibilities, you may be contacted within six (6) months. Please provide your email address so we may follow up with you:

_____

What issues are you experiencing in your practice and/or professional responsibilities that could be addressed in future programming?

_____

_____

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New Jersey HIVLinks Summer 2016
HIV, STD, and TB news and information for health professionals

Chronic Obstructive Pulmonary Disease in the HIV-Infected Population

Jennifer Williams, MD, MHA, Pulmonary Critical Care Medicine Fellow; Rutgers New Jersey Medical School, Amee Patrawalla, MD, MPH, Assistant Professor of Medicine, Director; Pulmonary Disease/Critical Care Training Program Rutgers New Jersey Medical School, Diego Caceres, MD, Pulmonary Critical Care Medicine Fellow; Rutgers New Jersey Medical School.

Purpose of review

While there has been improvement in HIV-related pulmonary infectious complications since the introduction of antiretroviral therapy, there is growing recognition of non-infectious lung diseases such as chronic obstructive pulmonary disease (COPD), which may impact overall outcome. We summarize what is known about the epidemiology and pathophysiology of COPD in HIV, as well as risk factors and treatment in HIV-related COPD.

Clinical case

A 68 year old active cigarette smoker, with a past medical history of HIV on antiretroviral therapy (ART), severe chronic obstructive pulmonary disease (COPD), coronary artery disease, and hypertension is admitted to the hospital with increased dyspnea, cough and purulent sputum. He has an undetectable viral load and CD4 count > 500 cells/microliter. He has had four prior hospital admissions, with intermittent use of steroids during that time, and is now taking prednisone 60 mg daily, and a course of antibiotics. He has good adherence to his medication regimen which consists of emtricitabine, tenofovir disoproxil fumarate, raltegravir, budesonide/formeterol inhaler, and albuterol inhaler as needed. What would be recommended for this patient at this point?

Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by airflow limitation that is not fully reversible, as defined by the Global Initiative on Obstructive Lung Diseases.[1] COPD is a systemic disease process associated with high morbidity and mortality.[2] With the advancement of treatment options for persons living with HIV (PLWH), longevity and survival rates have increased significantly over recent years. The increase in lifespan of PLWH has led to a growth in the prevalence of chronic conditions such as COPD. Furthermore, HIV has been found to be an independent risk factor for development of COPD.[2]

Epidemiology

In the pre-ART era, HIV-infected tobacco smokers were noted to have a higher rate of emphysema then controls (23% versus 2%).[3] HIV-associated emphysema was also seen in a much younger population compared to similar HIV-uninfected populations, where the disease tends to present after the age of 40. In addition, it has been found that HIV-infected non-smokers are also subject to an increased likelihood of COPD. While there is limited prospective data on HIV-associated COPD in the ART era, it appears HIV infection may carry a 50-60% higher risk of COPD.[4] This data is primarily based on self-report and diagnostic codes. Data from clinical trials measuring lung function also suggest that respiratory symptoms and airway obstruction are common. Interestingly, ART was an independent risk factor for airway obstruction.[4] Intravenous drug use (IDU) and tobacco use were also predictive of airway obstruction.[5] Other studies examining the prevalence and course of COPD in PLWH are ongoing.

HIV infection by itself has been shown to increase the incidence of COPD, linking the presence of a higher number of cytotoxic lymphocytes in the lungs when compared to HIV-uninfected patients. The addition of tobacco smoking significantly increases the rate of COPD in these patients.[3] Respiratory symptoms and pulmonary function abnormalities are common with diffusion impairment commonly encountered even in non-smokers.[6] The presence of COPD is associated with worse quality of life among PLWH. Screening of this at-risk population for COPD may lead to early intervention and improvement in overall health and quality of life.[7]

Other factors playing a role in the severity of disease are IDU and past or recurrent pulmonary infections. The prevalence of IDU is 22% of all PLWH in the United States (U.S.).[8,9] In the U.S., close to 8% of new HIV diagnoses in 2010 were among IDUs.[9] Infection with *Pneumocystis jiroveci* in particular is associated with COPD and accelerated decrease in lung function.[5]

One of the leading causes of mortality among PLWH is lung cancer. Although tobacco smoking rates account for some of the increased risk for lung cancer, HIV infection has been found to be an independent risk factor, with age of onset significantly earlier than the general population.[10] Mechanisms that could explain the increased risk for lung cancer among PLWH include the chronic state of inflammation, increased expression of proto-oncogenes and down regulation of the tumor suppressor gene.[10] COPD is an independent risk factor for lung cancer given its systemic effects and chronic airway inflammation. Inhaled corticosteroids have been considered as possible chemoprotective agents, however further research is being conducted.[11]

Pathophysiology

Studies suggest that HIV is an independent risk factor in COPD and acute exacerbations of COPD (ACOPD).[2] HIV infection is associated with heightened immune cell activation in the lung. There are increased numbers of cytotoxic T cells with CD8 T cell activation, CD4 T cell death receptor expression, and interleukins in bronchoalveolar lavage fluid (BALF), sputum, and serology of HIV-infected individuals.[12] More recently, it has been seen that loss of lung CD4 cells is evident in HIV associated COPD.[13] Tissue inflammation in COPD is exhibited primarily by neutrophils, CD8 lymphocytes, and macrophage infiltration with alterations in oxidative stress and apoptosis.[5] This type of induced inflammation causes accelerated parenchymal damage. HIV increases lung oxidative stress and thus augments pulmonary pathogenesis with increased prevalence of AECOPD in the setting of increased systemic inflammation.[14] Lower CD4 counts are associated with worse lung function and emphysema as seen on computed tomography (CT) scan, which lends credence to the idea that HIV increases the risk of COPD.[12]

Risk factors

There is an increased incidence of high-risk behaviors, such as tobacco smoking among PLWH.[5] Seventy-five percent of PLWH have smoked at least five packs of cigarettes in their lifetime, with half continuing as current tobacco smokers.[5] Approximately 19% of the general U.S. population are current cigarette smokers; the prevalence of tobacco smoking within the HIV-infected population is considerably higher, with recent studies reporting rates over 40%.[15,16] The highest prevalence of tobacco use occurs in HIV-infected men who have sex with men.[17]

Risk factors for AECOPD include CD4 counts < 350 cells/microliter and a RNA viral load >500 copies/ml.[14] Those with a detectable viral load were more likely to have active lung disease.[5] Lung function was worse in active tobacco smokers.[5]

Emphysematous changes with decreased diffusion capacity of the lung for carbon monoxide (DLCO), forced expiratory volume in one second (FEV1), and peak flow have also been found in PLWH with *Pneumocystis jiroveci* pneumonia both during and after an acute infection.[5] Furthermore, COPD is more prevalent as a population ages, and with the HIV population now living longer and with the cumulative exposure to tobacco smoke, these are likely some of the contributing factors to having an increase in the incidence of HIV-associated COPD.[4]

Clinical presentation

COPD has characteristic symptoms of dyspnea, chronic cough, and sputum production. Many individuals experience dyspnea on exertion with reported wheezing and chest tightness during acute exacerbations. Those that experience fatigue may attempt to modify lifestyle to reduce episodes of exertional dyspnea.[18] Other illnesses such as asthma and heart failure have similar presentations that can lead to incorrect diagnoses. A lung exam for COPD may show decreased breath sounds with bilateral wheezing on auscultation, increased resonance to percussion indicating hyperinflation, and increased antero-posterior diameter of the chest, the "barrel-shaped chest".[18]

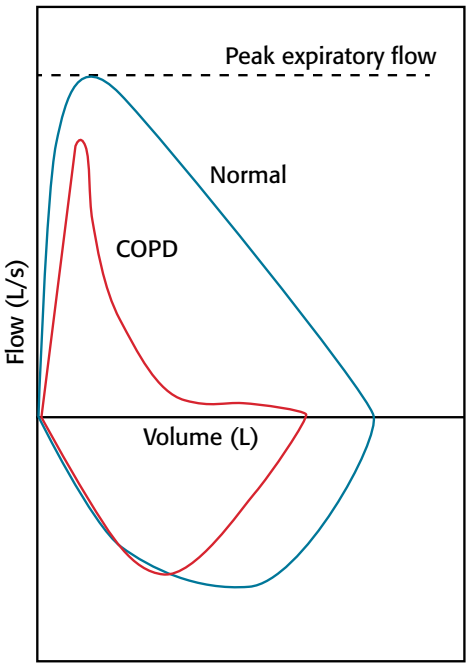
The diagnosis of COPD is based on spirometry, which demonstrates persistent airflow obstruction. Airflow limitation shows FEV1/forced vital capacity (FVC) ratio of less than 0.7, that is not fully reversible after inhaled bronchodilators.[19] Case control and prospective longitudinal studies have shown a decrease in overall lung function in the HIV-infected population with pulmonary function tests showing reduced FEV1 and DLCO.[5] Airway obstruction is worse in tobacco smokers, IDUs, and those on ART.[6]

Diagnosis

Arterial blood gas may show chronic respiratory acidosis and hypoxemia. In individuals <45 years with emphysema, a test for alpha-1 antitrypsin deficiency should be obtained.

Spirometry in COPD is abnormal with flow volume loop indicating irreversible airflow limitation. The expiratory limb of the flow volume loop is characteristically 'scooped'. FEV1 to FVC ratio is reduced. Severity of airflow limitation is generally determined by FEV1 (See Figure 1).

Figure 1: Flow Volume Loop for a Normal Patient (blue line) and a COPD patient (red Line)



McNulty W, Curtis K, Haji G. COPD - Meeting the diagnostic challenge. *British Journal of Family Medicine*, 2 6, November/December 2014.

Severity of airflow limitation in COPD (based on postbronchodilator FEV1)

In patients with FEV1/FVC <0.7:		
GOLD 1	Mild	FEV1 ≥80 percent predicted
GOLD 2	Moderate	50 percent ≤ FEV1 <80 percent predicted
GOLD 3	Severe	30 percent ≤ FEV1 <50 percent predicted
GOLD 4	Very severe	FEV1 <30 percent predicted

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO2) less than 60 mmHg (8 kPa) with or without arterial partial pressure of CO2 (PaCO2) greater than 50 mmHg (6.7 kPa) while breathing ambient air at sea level.

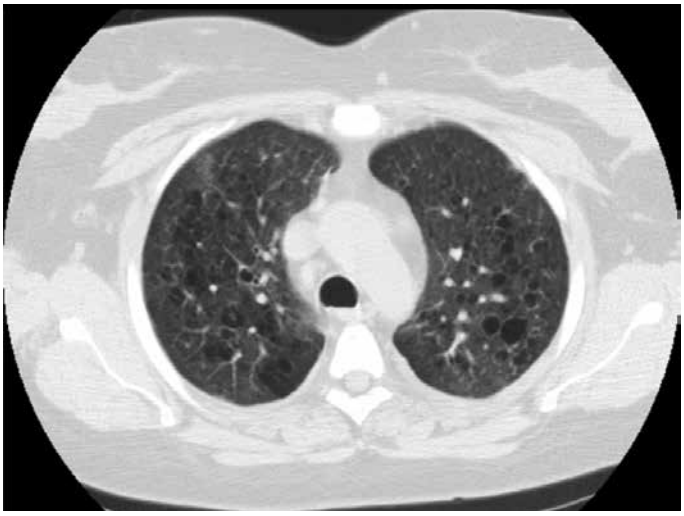
Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), www.goldcopd.org.

McNulty W, Curtis K, Haji G. COPD - Meeting the diagnostic challenge. *British Journal of Family Medicine*, 2 6, November/December 2014.

Imaging such as chest radiography may show hyperinflation, and is recommended to rule out complications such as pneumonia and/or pneumothorax.[19]

CT may show emphysematous changes in the lungs and can be performed to look at the extent of disease, bullae, infection, or assessment for lung volume reduction surgery. In addition to emphysema, CT of the chest in COPD may reveal bronchial wall thickening, bronchiolitis, and expiratory air trapping depending on COPD phenotype.[5]

Chest CT of a 44-year-old woman with HIV. She was receiving antiretroviral therapy, and her CD4 cell count was 479 cells/ml. Emphysema is seen with some areas of bullae.



Morris, George, Crothers, et al.: HIV and COPD. *Proc Am Thorac Soc Vol 8. pp 320–325, 2011DOI: 10.1513/pats.201006-045WR* Internet address: www.atsjournals.org

Additionally, CT can show if emphysema is centriacinar, seen predominantly in the upper lobes or panacinar emphysema which occurs at the lung bases and is usually associated with alpha-1-antitrypsin deficiency.[19] Additionally, paraseptal (distal acinar) emphysema shows small subpleural collections of air at the periphery and are often a precursor to bullae.[19]

Treatment

Active tobacco smoking in PLWH increases mortality, up to twice as much as non-tobacco smokers. Current HIV-infected tobacco smokers have more respiratory symptoms, COPD and more episodes of pneumonia.[20] In women smokers on ART, the risk for virologic rebound and more frequent immunologic failure appears higher.[21]

From a healthcare standpoint, tobacco smoking cessation is clearly the first priority in assisting PLWH with COPD. The USPSTF considers it a grade A recommendation that clinicians ask about tobacco use, advise about cessation and provide behavioral and pharmacologic interventions. The latter may include varenicline, bupropion and nicotine replacement therapy in various forms.[22] There is a warning that use of ritonavir, nelfinavir and efavirenz may alter the level of bupropion (either increase or decrease) leading to either adverse events or lower efficacy.[23,24] Both medications, bupropion and varenicline are considered to be comparably safe to non HIV-infected individuals.[25]

A tobacco smoking cessation program implemented in a large, local ID practice identified a 50% prevalence of tobacco smoking in their population. Of those who participated in the program, which included dedicated counseling and

continued on next page

pharmacologic therapy, 16% had a 6-month abstinence rate, comparable to other studies.[26] Clearly, tobacco smoking cessation efforts and innovative approaches must remain a priority in such at-risk populations.

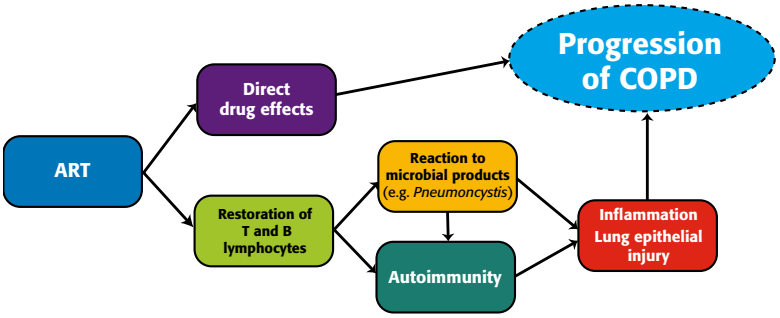
Initial Pharmacologic Management of COPD

Group	1st choice	Alternative	Other
A	Short-acting Anticholinergic prn or Short-acting beta2-agonist prn	Long-acting anticholinergic or Long acting beta2-agonist or Short-acting beta2 agonist and short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic or Long acting beta2-agonist	Long-acting anticholinergic and Long acting beta2-agonist	Short-acting beta2 agonist and/or Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting beta2-agonist or Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta2-agonist or Long-acting anticholinergic and phosphodiesterase-4 inhibitor or Long-acting beta2-agonist and phosphodiesterase-4 inhibitor	Short-acting beta2 -agonist and/or Short-acting anticholinergic Theophylline
D	Inhaled corticosteroid + long-acting beta2-agonist and/or Long-acting anticholinergic	Inhaled corticosteroid + long-acting beta2 -agonist and long-acting anticholinergic or Inhaled corticosteroid + long-acting beta2 -agonist and PDE-4 inhibitor or Long-acting anticholinergic and long-acting beta2 -agonist or Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine N-acetylcysteine Short-acting beta2 -agonist and/or Short-acting anticholinergic Theophylline

Adapted from: Global Initiative for Chronic Obstructive Pulmonary Disease, Executive Summary: Global Strategy for the Diagnosis, Management, and Prevention of COPD (Updated 2016)

Treatment of COPD includes non-pharmacologic and pharmacologic measures in a step wise approach. It is well known that age of tobacco smoking onset, total pack years and current smoking status influence COPD mortality.[27] Tobacco smoking cessation slows the rate of decline in lung function. Thus, tobacco smoking cessation efforts are a mainstay of COPD management. Addressing other substance use issues might also be necessary. Asymptomatic patients with COPD typically do not require disease-specific pharmacologic therapy.

Figure 2



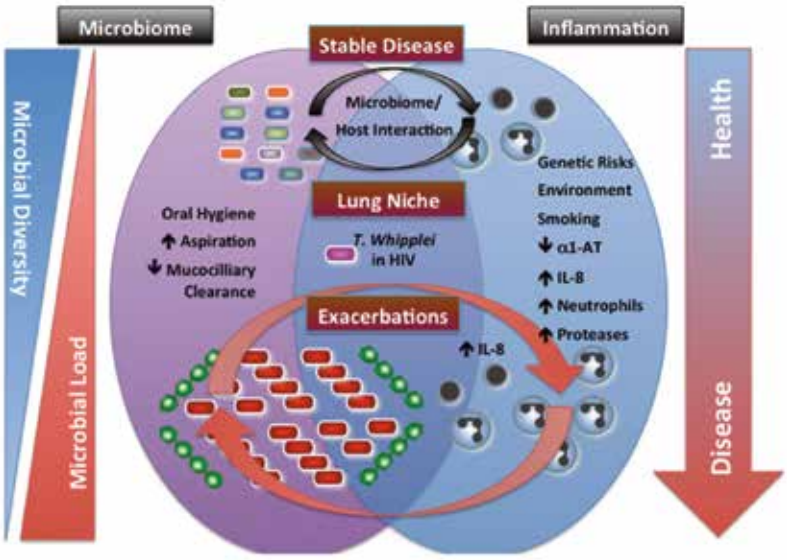
Morris A, George MP, Crothers K, et al. HIV and Chronic Obstructive Pulmonary Disease. Proceedings of the American Thoracic Society. 2011; 8(3):320-325.

Pharmacologic treatment of symptomatic patients with COPD includes bronchodilators given alone or in combination with inhaled glucocorticoids, depending on disease severity and therapy responsiveness. The GOLD guidelines categorize patients based on spirometry, risk of exacerbation, and symptoms.[1] Treatment is recommended based on the category each patient falls into, as depicted in the table above. For maintenance therapy, if required, longer acting medications and formulations are recommended. In several cohort studies, HIV-infected patients on ART were described as having lower responsiveness to bronchodilators.[4,7] In the pre-ART era, airway hyperresponsiveness and reactive airway disease were greater in untreated HIV-infected populations.[6,28] Higher viral loads and lower CD4 counts have been linked to greater odds of developing obstructive lung disease and worse lung function. It might then seem that treatment of HIV infection should lead to improved control of COPD or COPD prevention. In fact, ART has recently been associated with chronic medical conditions, including COPD. Hypotheses as to how this may occur are depicted in Figure 2. In one cohort study conducted at the University of Southern California HIV clinic in 2003, ART use was associated with lower FEV1/FVC ratio after controlling for tobacco smoking, age, IDU and history of pneumonia.[29] Similar to the effect on the cardiovascular system, it is presumed that ART leads to re-activation of the immune system, triggering inflammatory response to subclinical infections or development of autoimmunity potentiating airway obstruction.[30] Inhaled corticosteroids may then play an

important role in controlling disease and rates of exacerbations, however, it is also known that inhaled corticosteroids can increase the risk of pneumonia in COPD. Inhaled corticosteroids remain controversial in the management of COPD, both in HIV-infected and non-infected populations.

As noted previously, pulmonary infections and history of *Pneumocystis jiroveci* pneumonia contribute to disease severity, and we now know that there is a detectable change in pulmonary flora with disease severity. In a study using lung tissue samples from smokers and non-smokers, with stratification according to disease severity, those with severe obstructive disease had increased presence of Lactobacillus and Burkholderia. Smokers had more Actinobacteria.[31] Another study performed compared oral and airway microbiome in HIV-infected patients treated with antimicrobials after acute pneumonia, and demonstrated higher Proteobacterias, including *Klebsiella pneumoniae* and Pseudomonas species, which may explain higher prevalence of recurrent pneumonia.[32]

Figure 3. Conceptual model of the interaction between the lung microbiome and host immune response.



Segal, LN, Rom, WN, Weiden, MD. Lung microbiome for clinicians. New discoveries about bugs in healthy and diseased lungs. *Annals ATS Annals of the American Thoracic Society.* 2014;11(1):108–116.

Use of antibiotics in COPD has been shown to decrease the rates of hospitalization, exacerbations and improved quality of life.[33] Antibiotics may have some benefit in PLWH, but the impact of change in the lung microbiome is not known. As per Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for treatment, antibiotics are only recommended in patients with worsening dyspnea and cough who also have an increase in the volume of sputum and purulence, and not for patients with stable COPD.[1]

Roflumilast is a relatively new oral medication approved for COPD with chronic bronchitis and frequent AECOPD. It is a highly selective phosphodiesterase-4 inhibitor which appears to have beneficial anti-inflammatory effects. Gastrointestinal side effects may be treatment limiting. Roflumilast has not been specifically studied in PLWH.

Answer to clinical case: *This patient has severe COPD, with a history of frequent AECOPD despite being on a long-acting beta agonist, an inhaled corticosteroid and a short-acting beta agonist as needed. In addition to tobacco smoking cessation, the addition of a long-acting anticholinergic inhaler should be considered at this time. Outpatient pulmonary rehabilitation, shown to improve symptoms and reduce hospital readmission, would also be recommended.*

Conclusion

With the advancements in HIV treatment options, individuals are living longer, therefore there is an increasing prevalence of COPD in PLWH. There is a need to recognize, quantify and manage pulmonary complications such as COPD in this population. Further research to understand the underlying mechanisms associated with disease progression are needed. The high prevalence of COPD and ongoing tobacco smoking among PLWH highlights the importance of improving methods to help reduce known risk factors (see Figure 3). These efforts are essential in understanding and applying individualized patient-centered care. Reducing the rate of HIV-related COPD can alleviate healthcare costs and improve quality of life.

continued on next page

Figure 3. Behavioral and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: Clinical Summary.

Population	Nonpregnant adults ≥18 years	Pregnant women aged ≥18 years	Pregnant women aged ≥18 years	All adults aged ≥18 years
Recommendation	Provide pharmacotherapy and behavioral interventions for cessation Grade: A	Provide behavioral interveions for cessation. Grade: A	Pharmacotherpy interventions: No recommendation. Grade: I statement	Electronic nicotine delivery systems (ENDS): No recommendation. Grade: I statement

Assessment	The 5 A's framework is a useful strategy for engaging patients in smoking cessation discussions. The 5 A's include: 1) Asking every patient about tobacco use. 2) Advising all tobacco users quit, and 3) Arranging follow-up			
Behavioral Counseling Interventions	Behavioral interventions alone (in-person behavioral support and counseling, telephone counseling, and self-help materials) or combined with pharmacotherapy substantially improv achievement of tobacco cessation.	Behavioral interventions substantioally improve achievement of tobacco smoking abstinence, increase infant birthweight, and reduce risk for preterm birth.		
Pharmacotherpy interventions	Pharmacotherapy interventions, including Nicotine Replacement Therapy (NRT), bupropion sustained release (SR), and varenicline–with or without behavioral counseling interventions – substantially improve achievement of tobacco cessation.		There is inadequate or no evidence on the benefits of NRT, bupropion SR or varenicline to achieve tobacco cessation in pregnant women or improve perinatal outcomes in infants.	There is inadequate evidence on the benefit of ENDS to achieve tobacco cessation in adults or improve preinatal outcomes in infants.
Balance of Benefits and Harms	The USPSTF concludes with high certainty that the net benefit of hehavioral interventions and FDA-approved pharmacotherapy for tobacco cessation, alone or in combination, is substantial.	The USPSTF concludes with high certainty that the net benefit of hehavioral interventions for tobacco cessation on perinatal outcomes and smoking abstinence is substantial.	The USPSTF concludes that the evidence on pharmacotherapy interventions for tobacco cessation is insufficeint because of a lack of studies, and the balance of benefits and harms cannot be determined.	The USPSTF concludes that the evidence on the use of ENDS for tobacco cessation is insufficient and the balance of benefits and harms cannot be determined.
Other Relevant USPSTF Recommendations	The USPSFT recommends that primary-care clinicians provide interventions including education or brief counseling, to prevent the initiation of tobacco use in school-aged children and adolescents. This recommendation is available on the USPSFT website (www.uspreventiveservicestaskforce.org).			

Final Update Summary: Tobacco Cessation in Adults, including pregnant women: Behaviroal and Pharmacotherapy Interventions U.S. Preventive Services Task Force (USPSTF). September 2015.

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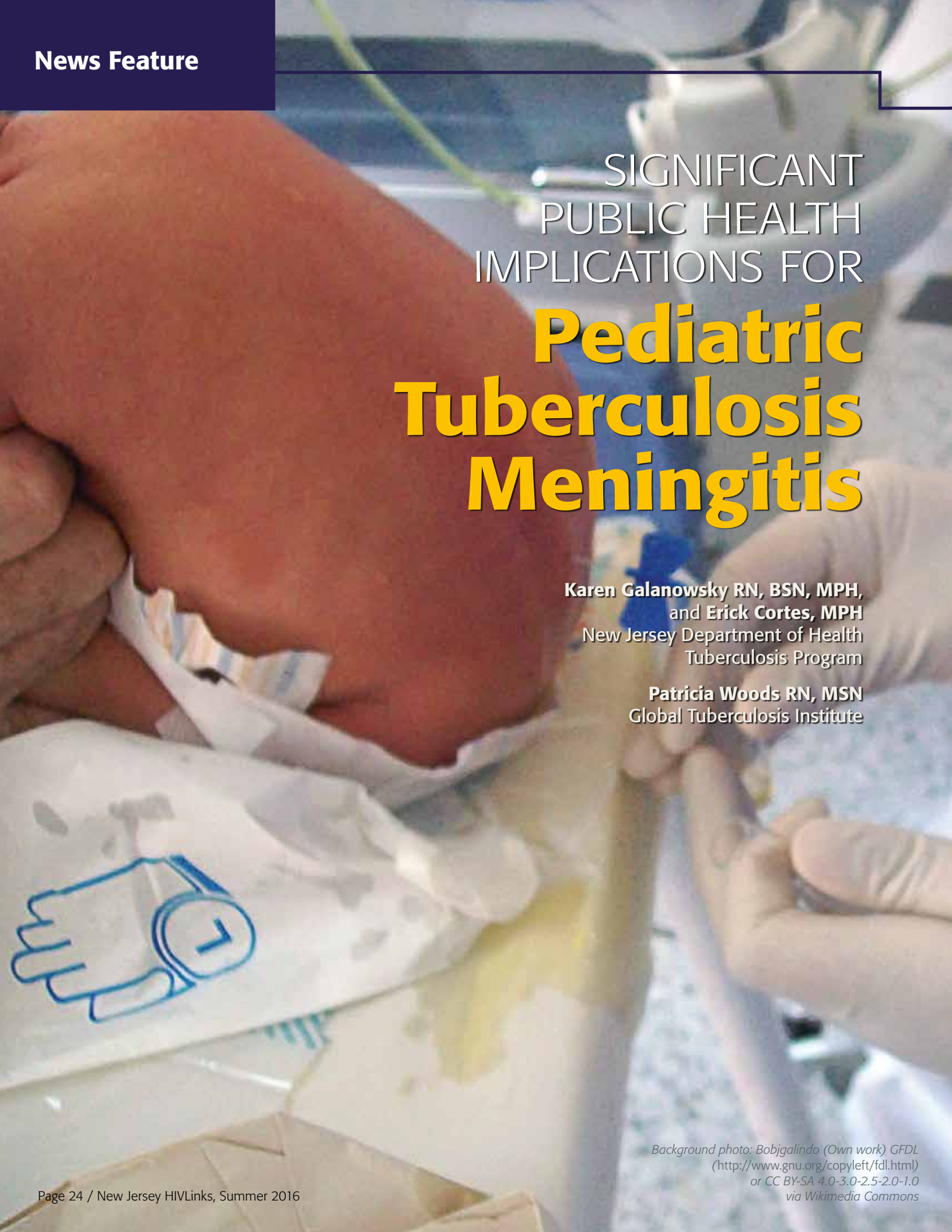

SIGNIFICANT PUBLIC HEALTH IMPLICATIONS FOR Pediatric Tuberculosis Meningitis

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Significant Public Health Implications for Pediatric Tuberculosis Meningitis

New Jersey HIVLinks Summer 2016
HIV, STD, and TB news and information for health professionals

Background

Between January 2013 and January 2015, seven cases of meningeal tuberculosis (TB) in children less than five years old were reported to the New Jersey Department of Health, TB Program. All seven children were United States born with foreign-born parents. Six of the seven parents were from countries where TB is endemic. All children were seen on multiple occasions by private pediatricians and emergency room (ER) physicians. Two of the children were admitted to the hospital with seizures. Four children were presumed to have upper respiratory tract infections with abnormal chest x-rays, fever, decreased appetite, and behavioral changes. The development of neurological deficits led to hospital admissions and the diagnosis of TB meningitis.

Methods

A retrospective review of the cases was conducted to find commonalities, identify reasons for delayed diagnosis, and treatment. The components for review included:

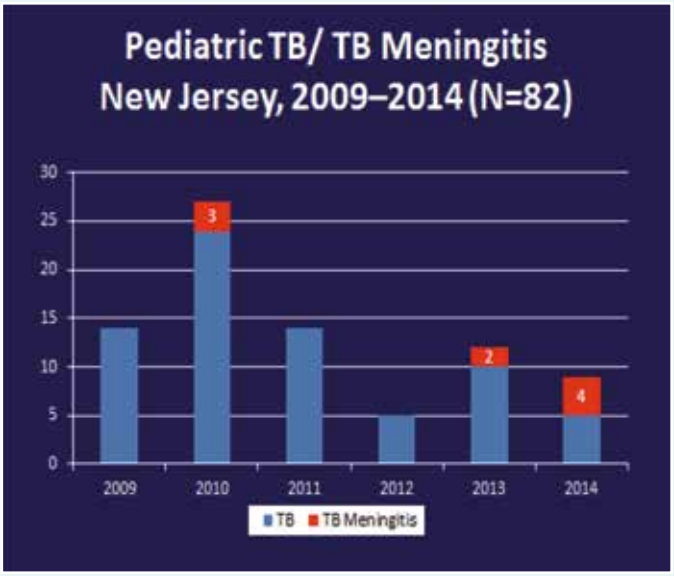
- role of TB nurse case manager and specialty TB pediatrician,
- collaboration and communication with physicians and hospitals,
- time from initial symptoms to diagnosis, hospitalization and treatment,
- TB medications prescribed and child's tolerance to medications, and
- Contact and source case investigations.

Genotyping results

A review of the circumstances surrounding delay in diagnosis was performed to identify the need for educational interventions in the private sector and ERs.

Results

Five/seven cases resided in six counties that were geographically dispersed throughout the state. Two children were siblings. Challenges identified by nurse case managers included: obtaining current information regarding the children's clinical status, tests performed and treatment during the hospitalization, plans for discharge, and direct observation therapy (DOT) while child received outpatient rehabilitation. Identification of one person in the hospital for information was important. Daily/weekly updates were critical to the outcomes. State TB nurse consultants facilitated communication and collaboration with a pediatric nurse practitioner and pediatric physician from the Global Tuberculosis Institute for consultation. The median time from onset of symptoms to diagnosis of TB meningitis was four months. All children initially presented with pulmonary symptoms thought to be pneumonia or asthma.



The graph above shows the six cases reported between 2013 and 2014. One additional case was reported in January 2015, bringing the total to seven cases.

Source cases were adult household contacts in five of seven children; confirmed by Restriction Fragment Length Polymorphism Assay (RFLP IS6110). The source case was not found in two of the seven cases.

The time between symptoms and diagnosis of TB meningitis illustrated the need for education to private and ER physicians. Meningeal involvement could have been prevented if TB had been diagnosed earlier. The need to reach private physicians statewide was apparent. A Public Health Alert email was sent to 2,600 physicians through the New Jersey Medical Society, American Academy of Pediatrics, and the American College of Emergency Physicians.

Source case was the child's mother who did not receive appropriate follow-up for TB disease by private physician. Child presented to the ER with vomiting, facial dropping and left sided hemiparesis. Inability to tolerate medication, INH resistance and inadequate treatment regimen resulted in multiple strokes and tuberculomas. NG tube was placed to administer TB medications. The child fully recovered after receiving 105 weeks of TB treatment, three hospitalizations and many months of outpatient physical therapy, occupational therapy, and speech therapy.

Conclusions

Pediatric meningitis is a sentinel event, indicating ongoing transmission and missed opportunities. Pediatric pulmonary TB and TB meningitis are difficult to diagnose, and are fre-

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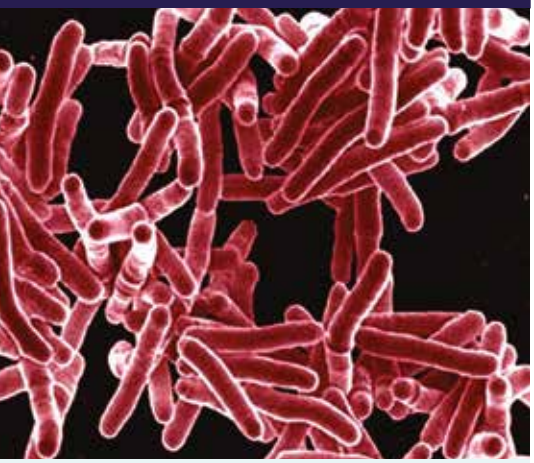

Photo above: Produced by the National Institute of Allergy and Infectious Diseases (NIAID), this digitally-colorized scanning electron micrograph (SEM) depicts a grouping of red-colored, rod-shaped Mycobacterium tuberculosis bacteria, which cause tuberculosis (TB) in human beings.

quently missed by private pediatricians and ER physicians who don't "think TB". Although seven cases over 24 months within a state is unusual, the contact investigations and genotyping results revealed that five/seven had no epidemiologic links. Effective and expedient public health activities were implemented in each event, and were instrumental in mitigating additional negative outcomes. The involvement of the nurse case management from the initiation of treatment was found to be a key factor in developing collaboration and communication with hospital staff, preventing negative clinical outcomes, and continuation of care post-hospitalization. Expert pediatric medical consultation and a pediatric nurse practitioner were utilized in all seven cases to meet the challenges of diagnostic and treatment modalities. The Public Health Alert sent to physicians throughout the state was the first educational effort to reach private and ER practitioners. Educational sessions were offered and provided. A poster was developed by the Global Tuberculosis Institute to remind practitioners in emergency rooms and private offices that TB may be a consideration in diagnosis. The poster was field tested with feedback and revision. It will be distributed by county TB Programs as a way to provide on-going education and collaboration. ❖

Partner Services: The Cornerstone of STD and HIV Prevention in New Jersey and Beyond

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STD Program, New Jersey Department of Health

They might be considered bounty hunters of STDs, professional bearers of bad news, or professional nosey neighbors. Each day, STD Disease Intervention Specialists (DIS) throw themselves into the trenches of the uncomfortable: Asking people to share intimate details about their health and sex lives and telling others of their exposure to an STD. While having such conversations with strangers is unthinkable for many, STD partner services continue to be a cornerstone of STD and HIV prevention throughout the country and in New Jersey.

An Effective Public Health Approach

The overall purpose of partner services is to locate and treat undiagnosed STD infections. This not only halts the spread of STDs, but also plays an important role in arresting disease progression to avoid negative outcomes (e.g., infertility, congenital syphilis, or neurosyphilis).[1] In addition to interviewing patients and locating their sexual partners, DIS also educates and counsels patients, refers them to additional medical or social services, and helps to identify and target at-risk communities. All this is done while adhering to stringent policies that ensure privacy and confidentiality for patients and their partners.[2]

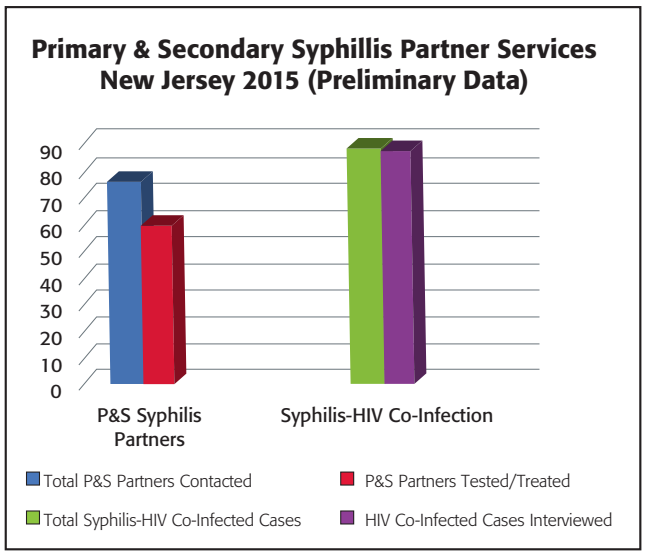
The partner services approach prevents patient reinfection while protecting privacy by providing a confidential means of contacting patients' sexual partners to refer them for screening and treatment. Even patients who wish to contact their partners themselves benefit from guidance and support from DIS to ensure that the notification is efficacious.

Once contacted by DIS, sexual partners of STD patients benefit from expeditious testing and treatment (temporary or ongoing) that prevents negative health outcomes and the further spread of disease. This is especially important because noticeable symptoms are the rarity in in STD and HIV cases, and therefore partners may not be aware of their exposure or risk prior to notification. Confidential partner services provide a process by which partners can be informed and educated about their risk, counseled about risk reduction strategies, receive medical care, and be linked to relevant services all before they have had any indication of their exposure, and possibly before they have had a chance to infect additional partners.

In addition, partner services programs benefit local communities by identifying undiagnosed cases as well as identifying higher risk groups within these communities. Partner services works in conjunction with surveillance efforts to identify areas that would benefit from targeted efforts such as screening at community venues and events, or "cluster interviewing" which identifies community members who have been exposed to an STD or HIV but have not been named through other partner notification processes.[3]

DIS Training

In order to successfully carry out the diverse set of partner services responsibilities and activities required of them, DIS typically undergo extensive formal and on the job training. CDC provides standard DIS training through regional training centers as well as additional "tracks" for different roles in STD prevention, such as providers who interview patients and refer to partner services and HIV-specific field staff. Extensive on the job training includes shadowing experienced DIS, and close supervision and review of assigned cases.



Partner Services in New Jersey

Each State in the country and the communities therein have unique needs with regards to the impact of STDs, and partner services activities can be tailored to meet these needs. Surveillance data from the State of New Jersey, STD Program inform allocations of resources as well as the development of policies, protocols and activities that target New Jersey areas and populations most affected by STDs. Given the sheer volume of reported STD cases in New Jersey (over 37,000 in 2014[4]), it is not feasible to track partners for every case, rather priority cases are followed by state and local health department DIS. Currently in New Jersey, this includes all infectious syphilis cases, as well as STD cases in patients 14 and under or who are pregnant.

Preliminary 2015 New Jersey STD data shows that DIS conducted interviews (including partner elicitation) with 85% of reported primary and secondary syphilis cases. In addition, 80% of partners subsequently contacted as a result of these interviews were successfully screened and/or treated for syphilis.[5]

Given the strong link between STD infection and HIV[6], New Jersey gives high priority to interviewing co-infected patients. Preliminary 2015 New Jersey data shows that 99% of patients co-infected with primary or secondary syphilis and HIV were interviewed.

Providers and Partner Services

Providers play an essential role in partner services. Health care providers are often the first ones to interact with a patient upon screening or diagnosis of an STD, may have already established a rapport with a patient, and therefore are in an optimal position to link a patient to partner services programs or even elicit information about their activities or partners. The provider can then work with DIS to determine appropriate ways to proceed with notification and treatment of partners. While partner services activities can still be initiated after a case is reported to the health department, research demonstrates that provider referral is often the most effective approach.[3] Regardless of how involved a provider is in the overall notification process, beginning this process immediately upon exam and/or diagnosis may halt the spread and progression of disease much faster than waiting until the health department receives a report and initiates an investigation.

Another partner services tool available to providers is Expedited Partner Therapy (EPT). EPT is a strategy whereby a health care provider who is treating a patient for an STD provides treatment for the patient's partner(s) without a medical evaluation. CDC endorses EPT as an option to facilitate treatment of male partners of women diagnosed with chlamydia or gonorrhea.[7] EPT is allowable under New Jersey State Administrative Code (N.J.A.C. 13:35-7.1)1 which states that health care providers may give medications or prescriptions without a medical examination when the health of the individual (or, with respect to a pregnant woman, the health of the woman or her unborn child) may be in jeopardy.[8]

Conclusions

Partner Services continue to be the cornerstone of STD prevention efforts and the benefits to patients, partners and communities have been well documented. There is no single universal best approach to partner services, rather the epidemiology of STDs as well as the needs and characteristics of target communities and populations inform the most appropriate and effective strategies for a given area. Regardless of the specific protocols chosen, close collaboration between providers and local health departments is essential for curbing the spread of STDs in an expeditious manner in order to minimize the impact on New Jersey's communities. ❖

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- New Jersey rapid testing site: www.state.nj.us/health/aids/rapidtesting
- New Jersey AIDS/STD Hotline: (800) 624-2377

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- Free online continuing education (CE) credits for healthcare professionals
- HIV/AIDS MEDICAL UPDATE SERIES: with funding from NJDHSS
- Free on-site HIV medical education for healthcare sites. Contact Michelle Thompson at (973) 972-1293 or ccthomps@sn.rutgers.edu

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- National Coordinating Resource Center: www.aidsetc.org
- Northeast/Caribbean AETC: www.nynjaetc.org
- National Clinician Consultation Center: http://www.nccc.ucsf.edu/
  HIV Warmline: (800) 933-3413
  Post-Exposure Prophylaxis Hotline/PEPline: (888) 448-4911
  Perinatal HIV Hotline: (888) 448-8765
  Pre-Exposure Prophylaxis Hotline (PrEPline): 888-HIV-PREP
  Substance Use Warmline: (855) 300-3595

AIDSinfo: a service of the U.S. Department of Health and Human Services, offers access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information. http://www.aidsinfo.nih.gov/

AIDS InfoNet: HIV treatment fact sheets in English and 10 other languages. www.aidsinfonet.org

U.S. National Institutes of Health: a registry and results database of publicly and privately supported clinical studies conducted around the world. http://clinicaltrials.gov

U.S. Centers for Disease Control and Prevention (CDC): http://www.cdc.gov/hiv/default.html

Health Resources and Services Administration (HRSA): http://www.hrsa.gov

FDA MedWatch: (800) FDA-1088; Subscribe to e-bulletin: www.fda.gov/medwatch/elist.htm

HealthHIV: Advances effective prevention, care and support for people living with, or at risk for, HIV by providing education, capacity building, health services research, and advocacy. http://www.healthhiv.org/index.php

National Quality Center: no-cost, technical assistance for Ryan White funded grantees to improve the quality of HIV care nationwide. www.nationalqualitycenter.org

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