Journal of
Medical Microbiology & Diagnosis

de Azevedo and Komninakis, J Med Microb Diagn 2014, 3:3
DOI; 10.4172/2161-0703.1000148

Review Article Open Access

HIV/HCV Coinfection: Considerations about Treatment

Rafael Gonçalves de Azevedo[1] **and Shirley Vasconcelos Komninakis**[1,2*]

[1]*Retrovirology Laboratory, Department of Infectious Diseases, Federal University of São Paulo, Brazil*

[2]*Laboratory of Molecular Biology - Lusíada Foundation, Santos - São Paulo, Brazil*

[*]**Corresponding author:** Shirley Vasconcelos Komninakis, Federal University of São Paulo, R. Pedro de Toledo, n. 781, São Paulo, Brazil, Tel: 551155764000; E-mail: skomninakis@yahoo.com.br

Rec Date: April 29, 2014, **Acc date:** July 14, 2014, **Pub date:** July 16, 2014

Abstract

Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) Infections are considered public health problems. The coinfection HIV/HCV is common in individuals exposed to parenteral exposure, and HVC has emerged as the leading cause of deaths among HIV-1-seropositive patients. The treatment of HIV/HCV coinfected people should be able to suppress viral replication for both viruses, with the purpose of to improve the immunological response and include liver damage. These two aspects should be associated with a high safety profile, because the toxicity of antiretroviral drugs used to treat HIV in HIV/HCV coinfected people, can lead them to death. The management of the treatment of patients is needed to monitor and, if possible, prevent complications related to adverse effects.

Keywords: HCV; HIV; Coinfection; Therapy

Introduction

Infection with Human Immunodeficiency Virus (HIV) currently affects over 33 million people worldwide and is considered a major public health problem worldwide [1,2]. Another important global pandemic is the infection by the hepatitis C virus (HCV), which affects around 3% of world population, approximately 180 million individuals [2-4].

Both HIV and HCV viruses are spread primarily by direct contact with infected blood. The main routes of transmission are blood transfusions not screened for HCV and / or HIV in the past, reuse of syringes, sharing of needles by intravenous drug users (IDUs), instruments for tattooing, piercing and placement used for manicures, sexual transmission and perinatal transmission [2,5,6].

How they divide the same route of transmission, coinfection with these viruses is not an uncommon event, especially among IDUs, where the rate of HCV infection in HIV-seropositive individuals with a history of injection drug use may be between 82 and 93% depending on the group studied. It is believed that about 4 to 5 million people in the world have HIV/HCV coinfection [7].

Analysis involved separate groups of HIV/HCV coinfected people, IDUs and multi-transfused hemophilia patients showed an increase viral load of HCV after HIV seroconversion. These studies showed a direct influence of coinfection with HIV and HCV on the natural history of HCV [8-10].

Other studies have shown that in HIV/HCV coinfected groups, liver inflammation is more intense than in patients HCV monoinfected, and the results of this event are the rapid progression of liver fibrosis and progression to liver disease, as cirrhosis and hepatocellular carcinoma in the most serious cases [11,12].

HIV infection has many influences on the progression of HCV in HIV/HCV coinfected people, but HCV also has influences on the progression of HCV in these patients. The low count of CD4 + T cells and the high viral load of HIV in HIV/HCV coinfected people are also associated with increased mortality from liver disease in AIDS patients [3,13-15].

The immune suppression caused by the HIV infection maybe is the main cause for the poor prognosis of HCV disease in coinfected patients. In acute HCV infection, T cells have an important role in controlling viremia to prevent progression to chronic phase. However, in coinfected individuals, the response of specific T cells is reduced, which facilitates the HCV replication in the beginning of infection [16,17]. Another essential factor is the functional change of natural killer cells and dendritic cells caused by HIV, because these cells play an important role in innate and adaptive immunity. Perhaps fact contributes to reduce the specific immune response against HCV during the course of HIV/HCV coinfection [18,19].

In chronic hepatitis by HCV, the immune system try to combat the infection by the activation of CD4+ and CD8+ T cells, which also happens during coinfection HIV/HCV, but with a lower level. Unfortunately we know that cellular activation does not increase during the course of coinfection, even with the gain of T cells and immune recovery through to HAART (Highly Active Antiretroviral Therapy) [20]. Liver injury in coinfection may also occur independently of immune suppression as a result of action of these viruses in the liver [7].

Over the past 50 years had a significant progress in developing specific and effective antiviral drugs. The major focus of antiviral research is the chronic infection by viruses such as HIV, Hepatitis B Virus (HBV) and HCV.

Initially, the drugs have been developed principally against viral enzymes. However, more recently the researchers have been developed drugs that inhibit the viral cycle steps and prevent events like virus entry. The current success is new drugs based on structure, function the molecular of viral proteins and mechanisms involved in the interactions between viruses and hosts.

The epidemic caused by HIV, a virus that causes chronic infection for a long period, brought the necessity to control this chronic infection with the development of drugs and new treatment strategies.

The discovery and development of drugs for HCV has progressed significantly in the last decade. Currently, individuals with chronic HCV infection are treated with pegylated interferon (PEG-IFN) and Ribavirin. Nowadays, about 56% of patients have a sustained virological response (SVR) at the end of treatment [3,21]. However, the assertion that the SVR results in viral clearance is controversial because there may be a hidden infection by HCV after SVR in the liver and various types of lymphoid cells (peripheral blood mononuclear cells, B cells and T) [22].

In the same time, developing of new drugs for HIV infection, the knowledge of the viral cycle is bringing new opportunities for therapeutic intervention and the first drugs specifically developed against enzymes of HCV are showing promising results. Despite all the progress in the treatment of HIV and HCV chronic carriers, there are considerable challenges, such as drugs effective against the wild virus and mutants that do not allow the resurgence of viral load, high bioavailability with a long elimination period, low doses that have simple administration (once daily) and all associated with a high safety profile with low toxicity (few adverse effects). Furthermore, the use of drugs combination regimens which not allowed the development of resistance.

After the introduction of HAART, there was a decrease of mortality caused by AIDS among patients with HIV Infection. On the other hand, there was an increase of mortality caused by liver disease in HIV/HCV coinfected people [7].

The current treatment for chronic monoinfected HCV patients is based on the administration of PEG-IFN and Ribavirin for 24 to 48 weeks. Depending of genotype the SVR rate is 50% [21,23]. Three randomized controlled studies, the APRICOT (AIDS Pegasys Ribavirin International Coinfection Trial), RIBAVIC and ACTG (AIDS Clinical Trial) compared the use of PEG-IFN with Ribavirin treatment with standard interferon with ribavirin in patients coinfected [24-26]. These three studies demonstrated that the HCV treatment is viable in HIV/HCV coinfected patients, but the treatment with PEG-IFN is better compared to standard treatment. SVR rates were 14% to 29% in patients with genotype 1 and 44% to 73% with genotypes 2 and 3. These SVR rates are generally lower than those published in studies with HCV monoinfected people, but the dose of ribavirin used in these three studies was lower than the commonly prescribed for monoinfected patients. In another study, the complete dose was prescribed and the response rates were still lower [27].

The kinetics of changes in the level of HCV in serum during treatment based on the INF has been studied. The parameters derived from mathematical models reflect the effectiveness of INF, the elimination rate of the cells and the rate of clearance of free virus [28]. In HIV/HCV coinfected patients in the first phase of decline (representing effectiveness) and the second phase slope (loss of infected cells) were similar to those HCV monoinfected patients, but clearance was lower [29]. HCV monoinfected people became HCV-RNA negative during treatment late, mainly due to the higher levels found before treatment (baseline). The dynamics of virological response has been used to guide the duration of treatment in these patients [30]. Similarly, studies with HIV/HCV coinfected patients showed initial virological response, that means HCV RNA-negative or a decrease of 2 log10 with respect to baseline at week 12, showing SVR [15,31].

As in HCV monoinfected patients, a SVR is associated with no progression of disease and related to liver histological improvement, which reduces the occurrence of liver decompensation or hepatocarcinoma [32-34]. The HCV genotypes are related to a better SVR after treatment. Individuals infected with genotype 2 and 3 show better response than individuals infected with genotypes 1 and 4.

Although antiviral therapy for HCV is effective in coinfected patients, this treatment is also associated with an increased risk of complications. The interaction of ribavirin with other nucleoside reverse transcriptase inhibitors can cause mitochondrial toxicity and mortality [35]. This syndrome has been found in patients treated with didanosine (ddI) and can be resolved discontinuing the use of nucleoside reverse transcriptase inhibitor [36].

The hepatic decompensation is another potential complication of treatment with interferon and ribavirin in coinfected patients. Although relatively rare (1.5% to 2%) is associated with high mortality in patients with cirrhosis, hyperbilirubinemia and to use ddI contributes to these risk factors [37,38].

Probably ribavirin has a synergistic effect with DDI for in vitro inhibition replicationf. This drug can interact with others antiretrovirals. Ribavirin, in vitro, antagonizes the effect of zidovudine (AZT) in HIV replication, while the use of AZT in patients receiving PEG-INF and ribavirin is associated with a higher rate of anemia [3,9,39,40].

Another important effect is the hepatotoxicity that appeared after the advent of HAART. Mechanisms of hepatotoxicity caused by HAART have not seemed to differ between HCV monoinfected patients and HCV/HIV coinfected. The development of liver lesion is result of immune reconstitution mediated by aggravation of the hepatocytes infected by HCV [41].

Risk factors for hepatotoxicity in coinfected patients on antiretroviral therapy include preexisting fibrosis and genotype 3 [42,43]. Any specific combination of medication has been associated with liver injury in patients coinfected, thus the selection of HAART would be based on other factors. The successful of HCV clearance by treatment with INF plus Ribavirin and SVR is associated with reduced risk of hepatotoxicity induced by HAART [44].

Some studies have shown a new marker for progression of liver fibrosis in HCV monoinfected and HIV/HCV coinfected patients. There is single nucleotide polymorphisms (SNPs) found in chromosome 19, specifically in the gene that encoded interleukin 28B (IL28B). The IL28B is a cytokine that plays an important role in the adaptive immune response against viral infections [45].

Currently, with the knowledge and development of molecular biology techniques and bioinformatics tools, it becomes clear the importance of the presence of some polymorphisms and different models of gene expression in the human genome, which may be linked to better or poorer response to treatment, a better immune response and other factors. The presence of the polymorphism and differential gene expression may be directly related to different ethnic groups.

In fact, a direct influence on SVR in HCV monoinfected and HIV/HCV coinfected individuals. It is the presence of a polymorphism in the gene that encodes a protein with interleukin activity of and it was called IL28B or INF lambda. It was demonstrated the presence of

the rs12979860 polymorphism is correlated with the SVR on treatment by INF and ribavirin. The ethnicity is another factor, which Caucasians responded better than Africans [46-49].

These studies showed that the development of new antiviral drugs and new treatment strategies need more studies to evaluate the interactions between host and virus to search genetic markers that can be used as predictors of response to these drugs.

Since the beginning of 2010, it has been shown the influence of treatment on prognosis for HCV monoinfected and HIV/HCV coinfected individuals, suggesting the use of laboratory marker in clinical practice and the development of a synthetic IL28B by pharmaceutical companies in the future with purpose of use in therapy these patients [46,47].

But in the future has a trend of marker IL28B not be necessary in clinical practice because the use of telaprevir and boceprevir in the treatment. Telaprevir and boceprevir are new protease inhibitors specific to the HCV nonstructural 3/4A serine protease. These new approaches may increase the rate of clearance virus in HCV monoinfected patients [50-53].

Two clinical trials PROVE1 and PROVE2 showed that the therapy duration can be reduced from 48 weeks to 24 weeks for most patients while maintaining an improved SVR with genotype 1 HCV, although with higher rates of discontinuation because of adverse events. In these studies, the rate of SVR was approximately 40% in the standard therapy group (PEG-IFN with ribavirin), 60% in the telaprevir group (PEG-IFN with ribavirin plus telaprevir) treated for 24 weeks and 68% in the telaprevir group treated for 48 weeks. Other important results were an increase in the rate of RVR at week 4 and a low subsequent rate of relapse, with telaprevir-based treatment as compared with standard therapy [50,51].

With these new drug in clinical practice, will be possible a combination therapy with ribavirin, removing the PEG-IFN of standard therapy and perform therapeutic schemes, like in HAART.

References

1. Bani-Sadr F, Carrat F, Pol S, Hor R, Rosenthal E, et al. (2005) Risk factors for symptomatic mitochondrial toxicity in HIV/hepatitis C virus-coinfected patients during interferon plus ribavirin-based therapy. J Acquir Immune Defic Syndr :47-52.
2. Bani-Sadr F, Carrat F, Rosenthal E, Piroth L, Morand P, et al. (2005) Spontaneous hepatic decompensation in patients coinfected with HIV and hepatitis C virus during interferon-ribavirin combination treatment. Clin Infect Dis 41:1806-1809.
3. Barreiro P, Labarga P, Martin-Carbonero L, Amor A, Ruiz-Sancho A, et al. (2006) Sustained virological response following HCV therapy is associated with non-progression of liver fibrosis in HCV/HIV-coinfected patients. Antivir Ther 11:869-877.
4. Beld M, Penning M, Lukashov V, McMorrow M, Roos M, et al. (1998) Evidence that both HIV and HIV-induced immunodeficiency enhance HCV replication among HCV seroconverters. Virology 244: 504-512.
5. Bezerra C, Oliveira J (2007) Comparação do interferon alfa convencional com o interferon alfa peguilado no tratamento de pacientes com hepatite C crônica. Conscientiae Saúde 6:19-28.
6. Bica I, McGovern B, Dhar R, Stone D, McGowan K, et al. (2001) Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis 32: 492-497.
7. Bonacini M, Govindarajan S, Blatt LM, Schmid P, Conrad A, Lindsay KL, et al. (1999) Patients co-infected with human immunodeficiency virus and hepatitis C virus demonstrate higher levels of hepatic HCV RNA. J Viral Hepat 6:203-208.
8. Cao YZ, Dieterich D, Thomas PA, Huang YX, Mirabile M, et al. (1992) Identification and quantitation of HIV-1 in the liver of patients with AIDS. AIDS 6: 65-70.
9. Capa L, Soriano V, García-Samaniego J, Nuñez M, Romero M, et al. (2007) Influence of HCV genotype and co-infection with human immunodeficiency virus on CD4(+) and CD8(+) T-cell responses to hepatitis C virus. J Med Virol 79: 503-510.
10. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, et al. (2004) Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA 292: 2839-2848.
11. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, et al. (2004) Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 351: 451-459.
12. Danta M, Semmo N, Fabris P, Brown D, Pybus OG, et al. (2008) Impact of HIV on host-virus interactions during early hepatitis C virus infection. J Infect Dis 197: 1558-1566.
13. De Clercq E (2007) The design of drugs for HIV and HCV. Nat Rev Drug Discov 6: 1001-1018.
14. Dorrucci M, Pezzotti P, Phillips AN, Lepri AC, Rezza G (1995) Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. J Infect Dis 172: 1503-1508.
15. Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ (1994) Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. Blood 84:1020-1023.
16. Fauci AS, Mavilio D, Kottilil S (2005) NK cells in HIV infection: paradigm for protection or targets for ambush. Nat Rev Immunol 5: 835-843.
17. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, et al. (2002) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 347: 975-982.
18. García-Samaniego J, Rodríguez M, Berenguer J, Rodríguez-Rosado R, Carbó J, et al. (2001) Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. Am J Gastroenterol 96: 179-183.
19. Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, et al. (2009) Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 360: 1839-1850.
20. Hoofnagle JH, Seeff LB (2006) Peginterferon and ribavirin for chronic hepatitis C. N Engl J Med 355: 2444-2451.
21. Kilmarx PH (2009) Global epidemiology of HIV. Curr Opin HIV AIDS 4: 240-246.
22. Lafeuillade A, Hittinger G, Chadapaud S (2001) Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. Lancet 357: 280-281.
23. Laguno M, Murillas J, Blanco JL, Martínez E, Miquel R, et al. (2004) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS 18: F27-36.
24. Levy JA (2009) HIV pathogenesis: 25 years of progress and persistent challenges. AIDS 23: 147-160.
25. Lissen E, Clumeck N, Sola R, Mendes-Correa M, Montaner J, et al. (2006) Histological response to pegIFNalpha-2a (40KD) plus ribavirin in HIV-hepatitis C virus co-infection. AIDS 20: 2175-2181.
26. Low E, Vogel M, Rockstroh J, Nelson M (2008) Acute hepatitis C in HIV-positive individuals. AIDS Rev 10: 245-253.
27. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, et al. (2001) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 358: 958-965.
28. Mauss S, Valenti W, DePamphilis J, Duff F, Cupelli L, et al. (2004) Risk factors for hepatic decompensation in patients with HIV/HCV

coinfection and liver cirrhosis during interferon-based therapy. AIDS 18: F21-25.

29. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, et al. (2009) Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 360: 1827-1838.
30. Mira JA, Lopez-Cortes LF, Merino D, Arizcorreta-Yarza A, Rivero A, et al. (2007) Predictors of severe haematological toxicity secondary to pegylated interferon plus ribavirin treatment in HIV-HCV-coinfected patients. Antivir Ther 12:1225-1235.
31. Neumann AU, Lam NP, Dahari H, Gretch DR, Wiley TE, et al. (1998) Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 282: 103-107.
32. Nischalke H, Vogel M, Michalk M, Natterman J, (2010) Genetic variation in IL28B rs 12979860 and response to HCV-specific treatment in HCV/HIV co-infected patients. 45th Annual Meeting of the European Association for the Study of the Liver, Vienna, Austria.
33. Nunez M, Ocampo A, Aguirrebengoa K, Cervantes M, Pascual A, et al. (2008) Incidence of anaemia and impact on sustained virological response in HIV/HCV-coinfected patients treated with pegylated interferon plus ribavirin. J Viral Hepat 15:363-369.
34. Nunez M, Rios P, Martin-Carbonero L, Perez-Olmeda M, Gonzalez-Lahoz J, et al. (2002) Role of hepatitis C virus genotype in the development of severe transaminase elevation after the introduction of antiretroviral therapy. J Acquir Immune Defic Syndr 30: 65-68.
35. Operskalski EA, Kovacs A (2011) HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. Curr HIV/AIDS Rep 8: 12-22.
36. Payan C, Pivert A, Morand P, Fafi-Kremer S, Carrat F, et al. (2007) Rapid and early virological response to chronic hepatitis C treatment with IFN alpha2b or PEG-IFN alpha2b plus ribavirin in HIV/HCV co-infected patients. Gut 56: 1111-1116.
37. Piguet V, Steinman RM (2007) The interaction of HIV with dendritic cells: outcomes and pathways. Trends Immunol 28: 503-510.
38. Rallón NI, Naggie S, Benito JM, Medrano J, Restrepo C, et al. (2010) Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients. AIDS 24: F23-29.
39. Rallón NI, Soriano V, Naggie S, Restrepo C, Goldstein D, et al. (2011) IL28B gene polymorphisms and viral kinetics in HIV/hepatitis C virus-coinfected patients treated with pegylated interferon and ribavirin. AIDS 25: 1025-1033.
40. Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, et al. (2010) Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology 138: 1338-1345, 1345.
41. Rotman Y, Liang TJ (2009) Coinfection with hepatitis C virus and human immunodeficiency virus: virological, immunological, and clinical outcomes. J Virol 83: 7366-7374.
42. Salmon-Ceron D, Lewden C, Morlat P, Bévilacqua S, Jougla E, et al. (2005) Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol 42: 799-805.
43. Seden K, Back D, Khoo S (2010) New directly acting antivirals for hepatitis C: potential for interaction with antiretrovirals. J Antimicrob Chemother 65: 1079-1085.
44. Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, et al. (2003) IL-28, IL-29 and their class II cytokine receptor IL-28R. Nat Immunol 4: 63-68.
45. Sherman KE, Shire NJ, Rouster SD, Peters MG, James Koziel M, et al. (2005) Viral kinetics in hepatitis C or hepatitis C/human immunodeficiency virus-infected patients. Gastroenterology 128: 313-327.
46. Soriano V, Maida I, Núñez M, García-Samaniego J, Barreiro P, et al. (2004) Long-term follow-up of HIV-infected patients with chronic hepatitis C virus infection treated with interferon-based therapies. Antivir Ther 9: 987-992.
47. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengoechea M, Hernandez-Quero J, et al. (1997) Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 26: 1-5.
48. Stone SF, Lee S, Keane NM, Price P, French MA (2002) Association of increased hepatitis C virus (HCV)-specific IgG and soluble CD26 dipeptidyl peptidase IV enzyme activity with hepatotoxicity after highly active antiretroviral therapy in human immunodeficiency virus-HCV-coinfected patients. J Infect Dis 186: 1498-1502.
49. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, et al. (2009) Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 41: 1105-1109.
50. Tencate V, Sainz B Jr, Cotler SJ, Uprichard SL (2010) Potential treatment options and future research to increase hepatitis C virus treatment response rate. Hepat Med 2010: 125-145.
51. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, et al. (2000) The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 284: 450-456.
52. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-García J, et al. (2004) Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 351: 438-450.
53. Torti C, Lapadula G, Puoti M, Casari S, Uccelli MC, et al. (2006) Influence of genotype 3 hepatitis C coinfection on liver enzyme elevation in HIV-1-positive patients after commencement of a new highly active antiretroviral regimen: results from the EPOKA-MASTER Cohort. J Acquir Immune Defic Syndr 41: 180-185.