A subset of older people is at increased risk of hospitalization and dependency. Emerging evidence suggests that immunosenescence reflected by an inverted CD4:8 ratio and cytomegalovirus (CMV) seropositivity plays an important role in the pathophysiology of functional decline. Nevertheless, the relation between CD4:8 ratio and functional outcome has rarely been investigated. Here, CD4:8 ratio and T-cell phenotypes of 235 community-dwelling persons aged >81.5 years in the BELFRAIL study and 25 younger persons (mean age 28.5 years) were analyzed using polychromatic flow cytometry. In the elderly persons, 7.2% had an inverted CD4:8 ratio, which was associated with CMV seropositivity, less naive, and more late-differentiated CD4+ and CD8+ T cells. However, 32.8% had a CD4:8 ratio >5, a phenotype associated with a higher proportion of naive T cells and absent in young donors. In CMV seropositives, this subgroup had lower proportions of late-differentiated CD4+ and CD8+ T cells and weaker anti-CMV immunoglobulin G reactivity. This novel naive T-cell-dominated phenotype was counterintuitively associated with a higher proportion of those with impaired physical functioning in the very elderly people infected with CMV. This underscores the notion that in very elderly people, not merely CMV infection but also the state of its accompanying immune dysregulation is of crucial importance with regard to physical impairment.

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UNLABELLED: Human immunodeficiency virus (HIV) and hepatitis virus coinfection amplify and accelerate hepatic injury. MicroRNAs (miRNAs) are small regulatory RNAs suggested as biomarkers for liver injury. We analyzed the circulating levels of miRNAs in HIV patients with regard to the extent and etiology of liver injury. Total RNA was extracted from 335 serum samples of HIV patients and 22 healthy control participants using Qiazol. Comprehensive polymerase chain reaction (PCR) array analyses (768 miRNA) were performed in serum samples of eight HIV, eight HIV/HCV (hepatitis C virus), six HCV patients, and three healthy controls. Reverse transcription (RT)-PCR measured levels of miRNA-122, miRNA-22, and miRNA-34a in serum samples of 335 patients and 19 healthy control participants. Liver injury and fibrosis in these patients were defined using aspartate aminotransferase (AST) levels, fibrosis-4 (FIB-4) index and AST-to-platelet ratio index (APRI) score. The miRNA pattern of HIV/HCV samples showed altered expression of 57 and 33 miRNA compared to HCV and HIV infection, respectively. miRNA-122, miRNA-22, and miRNA-34a were highly up-regulated in HIV/HCV patients. Analyzing the entire cohort, these miRNAs were correlated with liver function tests and were independent predictors of liver injury (AST >2 x ULN). miRNA-122 and miRNA-22 were associated with relevant fibrosis (FIB-4 >1.45; APRI >1). Circulating levels of miRNA-122 were independent predictors for relevant fibrosis in HIV patients. Interestingly, miRNA-122 and miRNA-34a levels were higher in HIV/HCV patients, miRNA-22 levels were highest in HIV/HBV patients, and circulating levels of miRNA-34a correlated positively with illicit drug use and ethanol consumption. CONCLUSION: Circulating miRNA-122, miRNA-22, and miRNA-34a correlates with the etiology of liver injury in HIV patients. These biomarkers not only mirror different mechanisms of hepatic injury, but also are independent predictors of liver injury in HIV patients. Copyright © 2014 by the American Association for the Study of Liver Diseases.


Male sex workers who sell or exchange sex for money or goods encompass a very diverse population across and within countries worldwide. Information characterising their practices, contexts where they live, and their needs is limited, because these individuals are generally included as a subset of larger studies focused on gay men and other men who have sex with men (MSM) or even female sex workers. Male sex workers, irrespective of their sexual orientation, mostly offer sex to men and rarely identify as sex workers, using local or international terms.
instead. Growing evidence indicates a sustained or increasing burden of HIV among some male sex workers within the context of the slowing global HIV pandemic. Several synergistic facilitators could be potentiating HIV acquisition and transmission among male sex workers, including biological, behavioural, and structural determinants. Criminalisation and intersectional stigmas of same-sex practices, commercial sex, and HIV all augment risk for HIV and sexually transmitted infections among male sex workers and reduce the likelihood of these people accessing essential services. These contexts, taken together with complex sexual networks among male sex workers, define this group as a key population underserved by current HIV prevention, treatment, and care services. Dedicated efforts are needed to make those services available for the sake of both public health and human rights. Evidence-based and human rights-affirming services dedicated specifically to male sex workers are needed to improve health outcomes for these men and the people within their sexual networks. Copyright © 2015 Elsevier Ltd. All rights reserved.


Sex work occurs in many forms and sex workers of all genders have been affected by HIV epidemics worldwide. The determinants of HIV risk associated with sex work occur at several levels, including individual biological and behavioural, dyadic and network, and community and social environmental levels. Evidence indicates that effective HIV prevention packages for sex workers should include combinations of biomedical, behavioural, and structural interventions tailored to local contexts, and be led and implemented by sex worker communities. A model simulation based on the South African heterosexual epidemic suggests that condom promotion and distribution programmes in South Africa have already reduced HIV incidence in sex workers and their clients by more than 70%. Under optimistic model assumptions, oral pre-exposure prophylaxis together with test and treat programmes could further reduce HIV incidence in South African sex workers and their clients by up to 40% over a 10-year period. Combining these biomedical approaches with a prevention package, including behavioural and structural components as part of a community-driven approach, will help to reduce HIV infection in sex workers in different settings worldwide. Copyright © 2015 Elsevier Ltd. All rights reserved.


(9) Chen TT, Chiu CF, Yang TY, Lin CC, Sargeant AM, Yeh SP, et al. *Hepatitis C infection is associated with hepatic toxicity but does not compromise the*
The influence of hepatitis C virus (HCV) infection on the outcome of patients with diffuse large B cell lymphoma (DLBCL) treated with rituximab-based chemotherapy is controversial. We retrospectively analyzed the characteristics and clinical outcomes of 168 patients with DLBCL diagnosed between January 2005 and December 2011. Twenty-nine patients who were HCV-positive before lymphoma treatment were compared with 139 patients who did not have HCV infection. The median follow-up duration was 3.0 (0.07-8.02) years. HCV infection resulted in more hepatic toxicity in both univariate (p=0.001) and multivariate (p=0.003) analyses. In addition, HCV-positive DLBCL patients were more likely to have treatment delay (20.1% vs. 0.7%, p<0.001). For patients who developed hepatic toxicity during immunochemotherapy, HCV-positive patients had significantly higher folds of aspartate aminotransferase elevation (p=0.042) and total bilirubin elevation (p=0.012) compared with those who were HCV negative. However, HCV did not influence the 5-year progression-free survival rate (p=0.412) or 5-year overall survival rate (p=0.410). In conclusion, HCV infection is associated with increased hepatic toxicity and delayed chemotherapy without compromised survival in DLBCL patients treated with rituximab-based chemotherapy. Copyright © 2014 Elsevier Ltd. All rights reserved.


BACKGROUND: Viremia copy-years (VCY) has been reported as a short-term predictor of mortality. We evaluated the association of this parameter with 10-year outcome within the APROCO-COPILOTE cohort. METHODS: Prospective data from 1281 HIV-1-infected patients who started a first protease inhibitor-containing regimen in 1997-1999 were analyzed. Patients with baseline plasma viral load (pVL) > 500 copies per milliliter and at least 2 pVL measures from the eighth month of follow-up were selected. VCY was calculated individually over the follow-up as the area under the pVL curve. Multivariate Cox models analyzed the relation between all-cause mortality and the following variables: age, sex, geographical origin, transmission group, HIV infection duration, ART-naive, pVL at baseline, time-dependent CD4 count, and VCY. RESULTS: Nine hundred seventy-nine patients were followed up for a median of 10 years (interquartile range: 5-11.5). At baseline, median (interquartile range) values for duration of HIV infection, pVL, and CD4 cell count were 43 (4-95) months, 4.6 (3.9-5.2) log10 copies per milliliter, and 278 (125-416) cells per cubic millimeter, respectively. At censoring date, 77 patients (8%) had died. VCY >1.4 log10 copies x yrs/mL was an independent predictor of death (hazard ratio: 2.0; 95% confidence interval: 1.2 to 3.5), which was no longer the case after adjustment for the latest pVL value [risk ratio (RR): 1.2 for 1 additional log10 copies per milliliter; 95% confidence interval: 1.1 to 1.4]. CONCLUSIONS: VCY was associated with mortality in HIV-infected patients under combined antiretroviral
therapy but did not overweigh the predictive value of the latest pVL. VCY might be more useful as a marker of persistent viral replication than for routine clinical care.


This report presents a molecular characterization of the complete genome of a rare hepatitis C virus (HCV) genotype (GT5a) from India. Sequence homology of full genome revealed that the strain belonged to HCV GT5a. To trace the origin of this virus and to understand its evolutionary pattern, a phylogenetic reconstruction was carried out on full HCV genome sequences using Bayesian coalescent methods. The phylogenetic tree reconstruction revealed genotypic divergence, with formation of distinct clades. This analysis revealed that HCV genotype 5 might have originated from HCV genotype 3, as they have a recent common ancestor.


BACKGROUND: Simultaneous splenectomy in liver transplantation (LT) is selectively indicated because of splenoportal venous thromboses and increased sepsis. Therefore, its impact should be further investigated. METHODS: Of the 160 liver transplant patients, only 40 underwent simultaneous splenectomy. Clinicopathologic characteristics and outcomes were compared between the splenectomy and non-splenectomy group using retrospective analysis. RESULTS: Although the groups were similar and had no significant difference in the intra- and postoperative data, non-splenectomy group had more male patients. However, splenectomy group showed significantly higher platelet and leukocyte counts at 1 month and 6 months after the transplantation and higher hepatitis C virus anti-viral therapy completion. Furthermore, 3 patients developed portal or splenic vein thrombosis during the postoperative follow-up, but the overall survival rate did not significantly differ between these groups. CONCLUSION: Simultaneous splenectomy in LT can be safely performed, particularly in patients with hepatitis C virus cirrhosis, small-for-size grafts, hypersplenism, and ABO blood group incompatible (ABO - incompatible) LT. Copyright © 2015 Elsevier Inc. All rights reserved.


BACKGROUND: Immigrant HIV-infected adults in industrialized countries show a poorer clinical and virologic outcome compared with native patients. We aimed to investigate potential differences in clinical, immunological, and virologic outcome in Dutch HIV-infected children born in the Netherlands (NL) versus born in Sub-Saharan Africa (SSA) in a national cohort analysis. METHODS: We included all HIV-
infected children registered between 1996 and 2013. Descriptive statistics, mixed-effects models, and Cox proportional hazard models were used to investigate differences between groups. RESULTS: In total, 319 HIV-infected children were registered. The majority of these children were born in SSA (n = 148, 47%) or NL (n = 113, 36%) and most were black (n = 158, 61%). Children born in NL were diagnosed at a median age of 1.2 years and initiated combination antiretroviral therapy (cART) at a median age of 2.6 years, compared with 3.7 and 5.3 years, respectively, for children born in SSA (HIV diagnosis: P < 0.001; cART initiation: P < 0.001). Despite a lower initial CD4 T-cell Z-score in children born in SSA, their immunological reconstitution was similar to children from NL. Virologic suppression was achieved in the majority of all cART-treated children (NL: 96%, SSA: 94%). There was no difference in the occurrence or timing of virologic failure.

CONCLUSIONS: Most immigrant HIV-infected children living in NL were born in SSA. Children born in SSA were diagnosed and initiated cART at an older age than children born in NL. Despite initial differences in CD4 T-cell counts and HIV viral load, the long-term immunological and virologic response to cART was similar in both groups.


Chronic Hepatitis B (HB) is the main risk factor for chronic liver disease (CLD) and hepatocellular carcinoma (HCC) in many low-resource countries, where diagnosis is constrained by lack of clinical, histopathological and biomarker resources. We have used proteomics to detect plasma biomarkers that outperform alpha-Fetoprotein (AFP), the most widely used biomarker for HCC diagnosis in low-resource contexts. Deep-plasma proteome analysis was performed in HCC patients, patients with CLD and in HB-carrier controls from Thailand (South-East Asia) and The Gambia (West-Africa). Mass spectrometry profiling identified latent-transforming growth factor beta binding-protein 2 (LTBP2) and Osteopontin (OPN) as being significantly elevated in HCC versus CLD and controls. These two proteins were further analyzed by ELISA in a total of 684 plasma samples, including 183 HCC, 274 CLD and 227 asymptomatic controls. When combined, LTBP2 and OPN showed an area under the receiver operating curve of 0.85 in distinguishing HCC from CLD in subjects with AFP <20 ng/mL. In a prospective cohort of 115 CLD patients from Korea, increased plasma levels of LTBP2 and/or OPN were detected in plasma collected over 2 years prior to diagnosis in 21 subjects who developed HCC. Thus, the combination of LTBP2 and OPN outperformed AFP for diagnosis and prediction of HCC and may therefore improve biomarker-based detection of HBV-related HCC. Copyright © 2014 UICC.


Highly active antiretroviral therapy (HAART) for the treatment of HIV infection sustains viral suppression and increases CD4(+) T cells in HIV patients. However, in 10-25% of subjects, known as immunological non-responders (INRs), HAART does not increase CD4 count. We investigated a potential role for galectin-9 and TIM-3 in INRs as galectin-9 and TIM-3 have been described to modulate NK and T cell function. PBMCs were isolated from healthy controls, HIV immunological responders (IRs, >350CD4(+) cells/mm(3)) and HIV INRs (<350CD4(+) cells/mm(3)) and TIM-3 and galectin-9 expressions on NK cell subsets and CD4(+) T cells were assessed. HIV INRs and HIV IRs showed increased galectin-9 expression on CD16(-)CD56(bright) and CD16(+)CD56(+) NK cells and CD4(+) T cells. Only HIV INRs showed a reduced frequency of TIM-3-expressing CD16(+)CD56(+), CD16(+)CD56(-) and CD4(+) cells, which correlated with low peripheral CD4 counts. These data suggest that TIM-3 expression may be characteristic for HIV INRs. Copyright © 2014 Elsevier Inc. All rights reserved.


BACKGROUND: Attendance at biannual medical encounters has been proposed as a minimum national standard for adequate engagement in HIV care. Using data from the HIV Outpatient Study, we analyzed how well dates of HIV-related laboratory testing correlated with attendance at biannual medical encounters. METHODS: HIV Outpatient Study is an open prospective cohort study of HIV-infected patients receiving outpatient care in the United States. The data set included dates for laboratory measurements and medical encounters. We included patients with at least 1 HIV laboratory test (CD4 cell count or plasma HIV RNA viral load) during 2010-2011. An HIV laboratory test was defined as associated with a medical encounter if it occurred within 3 weeks of the encounter. We assessed the predictive value of HIV laboratory tests as a proxy for adequate engagement in clinical care, defined as having had >2 HIV laboratory tests within 1 year and performed >90 days apart. RESULTS: A total of 10,321 HIV laboratory tests were recorded from 2909 patients. Adequate engagement in clinical care based on medical encounters was 88.2% and 77.3% when based on laboratory tests. Using HIV laboratory tests to assess engagement had a sensitivity of 85.7%, specificity of 86.0%, and positive and negative predictive values of 97.9% and 44.5%, respectively. Of the 22.7% classified as not engaged in care by the proxy measure, over half (55.5%) were actually engaged. CONCLUSIONS: Using laboratory monitoring reliably classified persons as engaged in care. Of the 22.7% of patients classified as not engaged in care, most were actually engaged.


The recognition of microbial patterns by Toll-like receptors (TLRs) is critical for activation of the innate immune system. Although TLRs are expressed by human CD4(+) T cells, their function is not well understood. Here we found that engagement of TLR7 in CD4(+) T cells induced intracellular calcium flux with activation of an anergic gene-expression program dependent on the transcription factor NFATc2, as well as unresponsiveness of T cells. As chronic infection with RNA viruses such as human immunodeficiency virus type 1 (HIV-1) induces profound dysfunction of CD4(+) T cells, we investigated the role of TLR7-induced anergy in HIV-1 infection. Silencing of TLR7 markedly decreased the frequency of HIV-1-infected CD4(+) T cells and restored the responsiveness of those HIV-1(+) CD4(+) T cells. Our results elucidate a previously unknown function for microbial pattern-recognition receptors in the downregulation of immune responses.


UNLABELLED: Sofosbuvir (Sovaldi, SOF) is a nucleotide analog prodrug that targets the hepatitis C virus (HCV) nonstructural protein 5B (NS5B) polymerase and inhibits viral replication. High sustained virological response rates are achieved when SOF is used in combination with ribavirin with or without pegylated interferon in subjects with chronic HCV infection. Potential mechanisms of HCV resistance to SOF and other nucleos(t)ide analog NS5B polymerase inhibitors are not well understood. SOF was the first U.S. Food and Drug Administration (FDA)-approved antiviral drug for which genotypic resistance analyses were based almost entirely on next-generation sequencing (NGS), an emerging technology that lacks a standard data analysis pipeline. The FDA Division of Antiviral Products developed an NGS analysis pipeline and performed independent analyses of NGS data from five SOF clinical trials. Additionally, structural bioinformatics approaches were used to characterize potential resistance-associated substitutions. Using protocols we developed, independent analyses of the NGS data reproduced results that were comparable to those reported by Gilead Sciences, Inc. Low-frequency, treatment-emergent substitutions occurring at conserved NS5B amino acid positions in subjects who experienced virological failure were also noted and further evaluated. The NS5B substitutions, L159F (sometimes in combination with L320F or C316N) and V321A, emerged in 2.2%-4.4% of subjects who failed SOF treatment across clinical trials. Moreover, baseline polymorphisms at position 316 were potentially associated with reduced response rates in HCV genotype 1b subjects. Analyses of these variants modeled in NS5B crystal structures indicated that all four substitutions could feasibly affect SOF anti-HCV activity. CONCLUSION: SOF has a high barrier to resistance; however, low-frequency NS5B substitutions associated with treatment failure were identified that may contribute to resistance of this important drug for chronic HCV infection. Copyright © Published 2014. This article is a U.S. Government work and is in the public domain in the USA.

BACKGROUND & AIMS: Twenty-four weeks of treatment with peginterferon and ribavirin for chronic hepatitis C virus (HCV) genotype 2 or 3 infection produces a sustained virologic response (SVR) in 70%-80% of patients. We performed a randomized, double-blind, phase 2b study to assess whether adding daclatasvir, a nonstructural protein 5A (NS5A) inhibitor that is active against these genotypes, improves efficacy and shortens therapy. METHODS: Patients with HCV genotype 2 or 3 infection (n = 151), enrolled at research centers in North America, Europe, or Australia, were assigned randomly to groups given 12 or 16 weeks of daclatasvir (60 mg once daily), or 24 weeks of placebo, each combined with peginterferon alfa-2a and ribavirin. Treatment was extended to 24 weeks for recipients of daclatasvir who did not meet the criteria for early virologic response. The primary end point was SVR at 24 weeks after treatment (SVR24). RESULTS: Baseline characteristics were similar among patients within each HCV genotype group. However, the 80 patients with HCV genotype 3, compared with the 71 patients with HCV genotype 2, were younger (mean age, 45 vs 53 y, respectively), and a larger proportion had cirrhosis (23% vs 1%, respectively). Among patients with HCV genotype 2 infection, an SVR24 was achieved by 83%, 83%, and 63% of those in the daclatasvir 12-week group, the daclatasvir 16-week group, or the placebo group, respectively; among patients with HCV genotype 3 infection, an SVR24 was achieved by 69%, 67%, and 59% of patients in these groups, respectively. Differences between genotypes largely were attributable to the higher frequency of post-treatment relapse among patients infected with HCV genotype 3. In both daclatasvir arms for both HCV genotypes, the lower bound of the 80% confidence interval of the difference in SVR24 rates between the daclatasvir and placebo arms was above -20%, establishing noninferiority. Safety findings were similar among groups, and were typical of those expected from peginterferon alfa and ribavirin therapy. CONCLUSIONS: Twelve or 16 weeks of treatment with daclatasvir, in combination with peginterferon alfa-2a and ribavirin, is a well tolerated and effective therapy for patients with HCV genotype 2 or 3 infections. Daclatasvir-containing regimens could reduce the duration of therapy for these patients. Clinicaltrials.gov number: NCT01257204. Copyright © 2015 AGA Institute. Published by Elsevier Inc. All rights reserved.


(23) Dyer C. Three men infected with hepatitis C through contaminated blood start legal proceedings against UK government. BMJ 2015 ;350( ):h302


During the last 30 years, there have been remarkable improvements in the treatment of patients with HIV. New drug regimens are both tolerable and easy to take, resulting in HIV viral suppression and markedly improved clinical outcomes. Viral suppression in patients with HIV significantly decreases the chance they will transmit the virus. Yet HIV transmission levels in the United States remain

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unacceptably high. Prevention efforts focused on HIV-negative persons who are at high risk for infection have led to the development of a pre-exposure prophylaxis (PrEP) strategy. This article provides an overview of PrEP and a review of the evidence for it, barriers to its use and how PrEP is being used in the United States and Minnesota. With concerted efforts by physicians, patients and public health authorities, PrEP could become a major tool in preventing transmission of the HIV virus.


Neurocognitive impairment still occurs in the era of HAART, though its onset appears to be delayed and its severity reduced, while HIV-infected individuals live longer with the infection. HAND defines three categories of disorders according to standardized measures of dysfunction: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). The pathogenic mechanisms underlying HAND involve host and virus characterizations and interactions and seem to depend heavily on the overall condition of the immune system. Since there are insufficient data at this point to determine the best therapeutic approach, and since HAART apparently is not sufficient to prevent or reverse HAND, therapy with a combination of drugs with high CPE should be considered while adjunctive and alternative therapies are being explored.


(29) Fauci AS, Marston HD. Focusing to achieve a world without AIDS. JAMA 2015 Jan 27;313(4):357-358


Occupational blood exposure (OBE) is a well-recognised hazard in the healthcare setting. A 4-year review of OBE in a large Irish teaching hospital over 2008-2011 found encouraging results, but identified deficits in documentation, communication and follow-up. The process was repeated 1 year later to determine if improvements were achieved and recommendations implemented. In 2012, 110 OBEs were reported, of which 81% were reported within 72 hours of the injury. The
administration of first aid was adequately documented in 85% of cases and confirmation of the provision of appropriate information and/or counselling in 72% of the cases. Attendance for follow-up was broadly in line with the previous review. The findings and recommendations contributed to improvements in practice. However, to ensure these are ongoing, the reinforcement of an educational strategy in a systematic way is fundamental.


OBJECTIVE: The antiviral efficacy of nucleos(t)ide analogues whose main limitation is relapse after discontinuation requires long-term therapy. To overcome the risk of relapse and virological breakthrough during long-term therapy, we performed a phase I/II, open, prospective, multicentre trial using a HBV envelope-expressing DNA vaccine. DESIGN: 70 patients treated effectively with nucleos(t)ide analogues for a median of 3 years (HBV DNA 120 IU/mL) or impossibility of stopping treatment at week 48. RESULTS: Reactivation occurred in 97% of each group after a median 28 days without liver failure but with an HBV DNA <2000 IU/mL in 33%; 99% of adverse reactions were mild to moderate. Immune responses were evaluated by enzyme-linked immunosorbent spot and proliferation assays: there was no difference in the percentage of patients with interferon- secreting cells and a specific T-cell proliferation to HBCAg but not to HBsAg after reactivation in each group.

CONCLUSIONS: Although it is fairly well tolerated, the HBV DNA vaccine does not decrease the risk of relapse in HBV-treated patients or the rate of virological breakthrough, and does not restore the anti-HBV immune response despite effective viral suppression by analogues. TRIAL REGISTRATION NUMBER: NCT00536627. Copyright Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions.


BACKGROUND: Although antiretroviral pre-exposure prophylaxis prevents HIV acquisition, it is not known if it alters HIV disease progression. This study assesses whether tenofovir gel impacted on disease progression among CAPRISA 004 microbicide trial seroconvertors. METHODS: Eighty-three seroconvertors from the tenofovir and placebo gel arms of the CAPRISA 004 trial were monitored.
prospectively for a minimum of 2 years by CD4 count and viral load (VL). Linear mixed models were fitted to HIV VL, and log rank test was used to compare time to reach CD4 counts of <350 cells per microliter. RESULTS: Median 2-week postinfection VL was 4.74 and 4.45 log copies per milliliter in women assigned to tenofovir gel (n = 32) and placebo gel (n = 51) (P = 0.189). Corresponding 12-month postinfection VLS were 4.24 and 3.70 log copies per milliliter (P = 0.016). After adjusting for clinical and behavioral characteristics and protective HLA alleles, mean VLS within the first 2 years were 4.51 and 4.02 log copies per milliliter in women from the tenofovir and placebo arms (P = 0.013). Among women with vaginal tenofovir measurements, mean VLS were 4.53 and 4.60 log copies per milliliter in those with detectable versus undetectable levels (P = 0.840). Overall mean CD4 counts were 463 and 514 cells per microliter in women assigned to tenofovir and placebo (P = 0.290). Thirty-two women (38.6%) reached CD4 counts of <350 cells per microliter at median 9.4 months postinfection, 13 (40.6%) from the tenofovir and 19 (37.3%) from the placebo arms (P = 0.786). CONCLUSIONS: Tenofovir gel had no impact on postinfection CD4 counts or the rate of CD4 decline. Although seroconvertors from the tenofovir arm experienced higher VLS, this did not result in a need for earlier antiretroviral therapy.


OBJECTIVE: Evaluate the risk of female breast cancer associated with HIV-CXCR4 (X4) tropism as determined by various genotypic measures. METHODS: A breast cancer case-control study, with pairwise comparisons of tropism determination methods, was conducted. From the Women's Interagency HIV Study repository, one stored plasma specimen was selected from 25 HIV-infected cases near the breast cancer diagnosis date and 75 HIV-infected control women matched for age and calendar date. HIV-gp120 V3 sequences were derived by Sanger population sequencing (PS) and 454-pyro deep sequencing (DS). Sequencing-based HIV-X4 tropism was defined using the geno2pheno algorithm, with both high-stringency DS [false-positive rate (3.5) and 2% X4 cutoff], and lower stringency DS (false-positive rate, 5.75 and 15% X4 cutoff). Concordance of tropism results by PS, DS, and previously performed phenotyping was assessed with kappa (kappa) statistics. Case-control comparisons used exact P values and conditional logistic regression. RESULTS: In 74 women (19 cases, 55 controls) with complete results, prevalence of HIV-X4 by PS was 5% in cases vs 29% in controls (P = 0.06; odds ratio, 0.14; confidence interval: 0.003 to 1.03). Smaller case-control prevalence differences were found with high-stringency DS (21% vs 36%, P = 0.32), lower stringency DS (16% vs 35%, P = 0.18), and phenotyping (11% vs 31%, P = 0.10). HIV-X4 tropism concordance was best between PS and lower stringency DS (93%, kappa = 0.83). Other pairwise concordances were 82%-92% (kappa = 0.56-0.81). Concordance was similar among cases and controls. CONCLUSIONS: HIV-X4 defined by population sequencing (PS) had good agreement with lower stringency DS and was significantly associated with lower odds of breast cancer.
OBJECTIVES: Even though multiple sclerosis (MS) and HIV infection are well-documented conditions in clinical medicine, there is only a single case report of a patient with MS and HIV treated with HIV antiretroviral therapies. In this report, the patient's MS symptoms resolved completely after starting combination antiretroviral therapy and remain subsided for more than 12 years. Authors hypothesised that because the pathogenesis of MS has been linked to human endogenous retroviruses, antiretroviral therapy for HIV may be coincidentally treating or preventing progression of MS. This led researchers from Denmark to conduct an epidemiological study on the incidence of MS in a newly diagnosed HIV population (5018 HIV cases compared with 50,149 controls followed for 31,875 and 393,871 person-years, respectively). The incidence rate ratio for an HIV patient acquiring MS was low at 0.3 (95% CI 0.04 to 2.20) but did not reach statistical significance possibly due to the relatively small numbers in both groups. Our study was designed to further investigate the possible association between HIV and MS. METHODS: We conducted a comparative cohort study accessing one of the world's largest linked medical data sets with a cohort of 21,207 HIV-positive patients and 5,298,496 controls stratified by age, sex, year of first hospital admission, region of residence and socioeconomic status and 'followed up' by record linkage. RESULTS: Overall, the rate ratio of developing MS in people with HIV, relative to those without HIV, was 0.38 (95% CI 0.15 to 0.79). CONCLUSIONS: HIV infection is associated with a significantly decreased risk of developing MS. Mechanisms of this observed possibly protective association may include immunosuppression induced by chronic HIV infection and antiretroviral medications.
newly diagnosed cases entering care within 90 days grew more rapidly in the post-law period. This is consistent with a positive effect of the law on entry to care.


BACKGROUND: The incidence of anal cancer has increased over the past 25 years, and HIV/HPV coinfection is the most important risk factor for anal squamous cell carcinoma. In this study, we demonstrated that the evaluation of systemic and compartmentalized anal mucosa immune response is relevant to differentiating HIV(+) patients at risk of anal intraepithelial neoplasia (AIN). METHODS: A systems biology approach was used to integrate different immunological parameters from anal mucosal tissue and peripheral blood assessed by phenotypic and intracytoplasmic analysis of lymphocytes and dendritic cell subsets. RESULTS: Our data demonstrated that anal mucosal mononuclear cells from AIN(+)/HIV(+) patients showed a robust capacity in producing proinflammatory/regulatory cytokines, mainly mTNF-alpha > IL-4 > IL-10 > IL-6 = IL-17A. Mucosal TNF-alpha/IFN-/IL-17A are selective high-grade squamous intraepithelial lesion (HSIL)-related biomarkers. Higher levels of circulating CD11cCD123cells and CD1a cells along with elevated levels of IFN-CD4 T cells are major features associated with HSIL in AIN(+)/HIV(+) patients. Regardless of the presence of AIN, HIV(+) patients presented a complex biomarker network, rich in negative connections. Among those patients, however, HSIL+ patients displayed stronger positive links between peripheral blood and anal mucosa environments, exemplified by the subnet of IL-17A/TNF-alpha/CD4IFN- /CD11cCD123 cells. CONCLUSIONS: The significant association between HSIL and the levels of TNF-alpha/IL-17A/IFN- along with the different subsets of DCs present in the anal mucosa milieu should be studied in more detail as a way to identify and categorize HIV(+) patients vis a vis the high risk of anal cancer outcome.


Viruses cause a wide range of human diseases, ranging from acute self-resolving conditions to acute fatal diseases. Effects that arise long after the primary infection can also increase the propensity for chronic conditions or lead to the development of cancer. Recent advances in the fields of virology and pathology have been fundamental in improving our understanding of viral pathogenesis, in providing improved vaccination strategies and in developing newer, more effective treatments.
for patients worldwide. The reviews assembled here focus on the interface between virology and pathology and encompass aspects of both the clinical pathology of viral disease and the underlying disease mechanisms. Articles on emerging diseases caused by Ebola virus, Marburg virus, coronaviruses such as SARS and MERS, Nipah virus and noroviruses are followed by reviews of enteroviruses, HIV infection, measles, mumps, human respiratory syncytial virus (RSV), influenza, cytomegalovirus (CMV) and varicella zoster virus (VZV). The issue concludes with a series of articles reviewing the relationship between viruses and cancer, including the role played by Epstein-Barr virus (EBV) in the pathogenesis of lymphoma and carcinoma; how human papillomaviruses (HPVs) are involved in the development of skin cancer; the involvement of hepatitis B virus infection in hepatocellular carcinoma; and the mechanisms by which Kaposi's sarcoma-associated herpesvirus (KSHV) leads to Kaposi's sarcoma. We hope that this collection of articles will be of interest to a wide range of scientists and clinicians at a time when there is a renaissance in the appreciation of the power of pathology as virologists dissect the processes of disease.

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BACKGROUND: Aberrant serum immunoglobulin G (IgG) glycosylation and its immunomodulatory effect are rarely addressed in chronic hepatitis B virus (HBV) infection. METHODS: Serum IgG-Fc glycosylation profiles in 76 patients with HBV-related liver cirrhosis and 115 patients with chronic hepatitis B (CHB) before and after 48 weeks of anti-HBV nucleos(t)ide analogue treatment were analyzed using high-throughput liquid chromatography-mass spectrometry and were compared to profiles in 108 healthy controls. RESULTS: The level of aberrant serum IgG-Fc glycosylation, particularly galactose deficiency, was higher in patients with CHB and those with cirrhosis (P < 0.001; odds ratio, 0.74; 95% confidence interval,.56-.97) and an Ishak fibrosis score of > 3 (odds ratio, 0.69; 95% confidence interval,.49-.97). Administration of antiviral therapy for 48 weeks reversed aberrant IgG-Fc glycosylation in patients with CHB from week 12 onward but did not reverse glycosylation in patients with cirrhosis. Attenuated IgG opsonization in patients with CHB, which was correlated with aberrant Fc-glycosylation, was reversed after treatment as well. CONCLUSIONS: Aberrant serum IgG-Fc glycosylation in CHB, which is highly associated with histological liver damage, affects IgG opsonizing activity and can be reversed by antiviral therapy. Copyright © The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.


(45) Hua J, Lin H, Ding Y, Qiu D, Wong F, He N. **HIV drug resistance in newly diagnosed adults in a rural prefecture of eastern China.** Epidemiology & Infection 2015 Feb;143(3):663-672

Little is known about HIV drug resistance (HIVDR) in newly diagnosed HIV-infected adults in eastern China where the HIV epidemic is spreading predominantly through sexual contact. During 2008-2011, newly HIV-diagnosed adults in Taizhou prefecture, Zhejiang province in eastern China were examined for HIVDR by amplifying and sequencing the HIV-1 pol gene. Of 447 genotyped participants, 537% were infected with CRF01_AE, 201% with CRF07_BC, 125% with subtype B, and 116% with CRF08_BC. Most of the participants had one or more minor genetic mutations in the pol gene that are associated with HIVDR. Twelve (27%) participants met the standard guidelines of having low to high HIVDR, suggesting that the prevalence of HIVDR in newly HIV-diagnosed adults was low in the study area and current antiretroviral therapy (ART) regimens are likely to remain effective. However, given high frequency of minor HIVDR in HIV patients and the scaling up of ART programmes in China, larger HIVDR surveillance programmes are needed.


**BACKGROUND:** Hepatocellular carcinoma (HCC) is strongly associated with hepatitis B virus (HBV) infection. False-negative results are common in routine serological tests and quantitative real-time PCR because of HBV surface antigen (HBsAg) variation and low HBV copy number. Droplet digital PCR (ddPCR), a next generation digital PCR, is a novel, sensitive, and specific platform that can be used to improve HBV detection. METHODS: A total of 131 HCC cases with different tumor stages and clinical features were initially classified with a serological test as HBsAg positive (n = 107) or negative (n = 24) for HBV infection. Next, DNA templates were prepared from the corresponding formalin-fixed paraffin-embedded (FFPE) tissues to determine HBV copy number by ddPCR. RESULTS: HBV copy numbers, successfully determined for all clinical FFPE tissues (n = 131), ranged from 1.1 to 175.5 copies/μL according to ddPCR. The copy numbers of HBV were positively correlated with tumor-nodes-metastasis (P = 0.008) and Barcelona-Clinic Liver Cancer (P = 0.045) classification. Moreover, serum cholinesterase correlated with hepatitis B viral load (P = 0.006). CONCLUSIONS: HBV infection is a key factor that influences tumorigenesis in HCC by regulating tumor occurrence and development. ddPCR improves the analytical sensitivity and specificity of measurements in nucleic acids at a single-molecule level and is suitable for HBV detection. Copyright © 2014 American Association for Clinical Chemistry.

Bacterial sepsis is an important cause of morbidity and mortality in patients with HIV. HIV causes increased susceptibility to invasive infections and affects sepsis pathogenesis caused by pre-existing activation and exhaustion of the immune system. We review the effect of HIV on different components of immune responses implicated in bacterial sepsis, and possible mechanisms underlying the increased risk of invasive bacterial infections. We focus on pattern recognition receptors and innate cellular responses, cytokines, lymphocytes, coagulation, and the complement system. A combination of factors causes increased susceptibility to infection and can contribute to a disturbed immune response during a septic event in patients with HIV. HIV-induced perturbations of the immune system depend on stage of infection and are only in part restored by combination antiretroviral therapy. Immunomodulatory treatments currently under development for sepsis might be particularly beneficial to patients with HIV co-infection because many pathogenic mechanisms in HIV and sepsis overlap. Copyright © 2015 Elsevier Ltd. All rights reserved.


BACKGROUND: Natural killer (NK) cell phenotype and function have recently gained much attention as playing crucial roles in antibody-dependent cellular cytotoxicity (ADCC). We investigated NK cell function, as measured by ADCC, in HIV-1-positive individuals before and 6 months after highly active antiretroviral therapy (HAART) initiation. METHOD: The ability of antibodies and NK cells to mediate ADCC was investigated separately and in combination in an autologous model. The NK cell subset distribution and NK cell phenotype (ie, expression of maturation and activation markers within NK cell subsets) were analyzed. RESULTS: The ability of NK cells to mediate ADCC was significantly increased after only 6 months of HAART and was not explained by a normalization of NK cell subsets (CD56 CD16 and CD56 CD16 NK cells) but rather by normalization in the frequency of NK cells expressing CCR7 and CD27. For individuals with no increase in ADCC after 6 months of HAART, the frequency of NK cells expressing NKp46 was downregulated. The ability of antibodies to mediate ADCC alone and in combination in an autologous model was not improved. CONCLUSIONS: HAART improves the ability of NK cells to mediate ADCC after 6 months. This improvement does not correlate with general immune restoration, as measured by CD4 T-cell counts, but rather to a decrease in the frequency of NK cells expressing CCR7 and CD27.


OBJECTIVE: Impaired adaptive response to oxidative injuries is a fundamental mechanism central to the pathogenesis of chronic hepatitis C (CHC). Glycogen...
synthase kinase (GSK) 3beta is an indispensable regulator of the oxidative stress response. However, the exact role of GSK3beta in CHC is uncertain and was examined. DESIGN: GSK3beta and Nrf2 signalling pathways were examined in JFH1 HCV infected Huh7.5.1 hepatocytes, and also in liver biopsy specimens from CHC patients. RESULTS: HCV infection elicited prominent Nrf2 antioxidant response in hepatocytes, marked by elevated expression of the Nrf2-dependent molecule haem oxygenase-1 and subsequent protection from apoptotic cell death. Inhibitory phosphorylation of GSK3beta seems to be essential and sufficient for HCV-induced Nrf2 response. Mechanistically, GSK3beta associated and physically interacted with Nrf2 in hepatocytes. In silico analysis revealed that Nrf2 encompasses multiple GSK3beta phosphorylation consensus motifs, denoting Nrf2 as a cognate substrate of GSK3beta. In the presence of TGFbeta1, the HCV-induced GSK3beta phosphorylation was blunted via a protein phosphatase 1-dependent mechanism and the cytoprotective Nrf2 response drastically impaired. This effect was counteracted by lithium, a selective inhibitor of GSK3beta. In liver biopsy specimens from CHC patients, the expression of phosphorylated GSK3beta positively correlated with Nrf2 expression and was inversely associated with the degree of liver injury. Moreover, CHC patients who received long-term lithium carbonate therapy primarily for concomitant psychiatric disorders exhibited much less liver injury, associated with enhanced hepatic expression of Nrf2. CONCLUSIONS: Inhibition of GSK3beta exerts hepatoprotection in CHC possibly through its direct regulation of Nrf2 antioxidant response.


Administration of combination antiretroviral therapy to human immunodeficiency virus type 1 (HIV-1)-infected pregnant women significantly reduces vertical transmission. In contrast, maternal co-opportunistic infection with primary or reactivated cytomegalovirus (CMV) or other pathogens may facilitate in utero transmission of HIV-1 by activation of cord blood mononuclear cells (CBMCs). Here we examine the targets and mechanisms that affect fetal susceptibility to HIV-1 in utero. Using flow cytometry, we demonstrate that the fraction of CD4(+)CD45RO(+) and CD4(+)CCR5(+) CBMCs is minimal, which may account for the low level of in utero HIV-1 transmission. Unstimulated CD4(+) CBMCs that lack CCR5/CD45RO showed reduced levels of HIV-1 infection. However, upon in vitro stimulation with CMV, CBMCs undergo increased proliferation to upregulate the fraction of T central memory cells and expression of CCR5, which enhances susceptibility to HIV-1 infection in vitro. These data suggest that activation induced by CMV in vivo may alter CCR5 expression in CD4(+) T central memory cells to promote in utero transmission of HIV-1. Copyright © The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
A community empowerment-based response to HIV is a process by which sex workers take collective ownership of programmes to achieve the most effective HIV outcomes and address social and structural barriers to their overall health and human rights. Community empowerment has increasingly gained recognition as a key approach for addressing HIV in sex workers, with its focus on addressing the broad context within which the heightened risk for infection takes places in these individuals. However, large-scale implementation of community empowerment-based approaches has been scarce. We undertook a comprehensive review of community empowerment approaches for addressing HIV in sex workers. Within this effort, we did a systematic review and meta-analysis of the effectiveness of community empowerment in sex workers in low-income and middle-income countries. We found that community empowerment-based approaches to addressing HIV among sex workers were significantly associated with reductions in HIV and other sexually transmitted infections, and with increases in consistent condom use with all clients. Despite the promise of a community-empowerment approach, we identified formidable structural barriers to implementation and scale-up at various levels. These barriers include regressive international discourses and funding constraints; national laws criminalising sex work; and intersecting social stigmas, discrimination, and violence. The evidence base for community empowerment in sex workers needs to be strengthened and diversified, including its role in aiding access to, and uptake of, combination interventions for HIV prevention. Furthermore, social and political change are needed regarding the recognition of sex work as work, both globally and locally, to encourage increased support for community empowerment responses to HIV. Copyright © 2015 Elsevier Ltd. All rights reserved.
response patients. Further, a significant increase in risk was also revealed for the CC genotype of IL-10 -592A/C in response-relapse patients or non-responder patients compared to sustained virological response patients, suggesting a role of the GG genotype of IL-10 -1082A/G and CC genotype of IL-10 -592A/C in the treatment outcome of combined Peg-IFN/ribavirin therapy.


(56) Kirchner JT. HIV: 3 cases that hid in plain sight. J.Fam.Pract. 2015 Jan;64(1):20-26

Having a high index of suspicion is key to recognizing the signs of HIV infection in patients without classic risk factors. How quickly would you have spotted these 3 cases?


To determine changes in incidence of reactivation of Toxoplasma gondii infection, manifesting as toxoplasmic encephalitis, and to assess the immunological mechanisms controlling reactivation in HIV-infected patients, a Czech cohort of 502 HIV/T. gondii co-infected patients was followed for 29093 person-years. The incidence of toxoplasmic encephalitis between the periods before and after the introduction of combination antiretroviral therapy (cART) was compared. Toxoplasmic encephalitis was diagnosed in 21 patients. In those patients the geometric mean value of CD4+ T lymphocytes was 126 times lower than in patients with non-reactivated T. gondii infection but an additionally significant decline in CD8+ T lymphocytes (33-fold) and natural killer cells (43-fold) was observed. This confirms the significance of these parameters. A twelvefold decrease in Toxoplasma reactivation incidence (402 vs. 34/1000 person-years) between monitored periods was seen. In the cART era, Toxoplasma reactivation was observed only in patients with unrecognized HIV infection or refusing therapy.


A successful treatment of AIDS world-wide is severely hindered by the HIV virus' drug resistance capability resulting from complicated mutation patterns of viral proteins. Such a system of mutations enables the virus to survive and reproduce despite the presence of various antiretroviral drugs by disrupting their binding capability. Although these interacting mutation patterns are extremely difficult to efficiently uncover and interpret, they contribute valuable information to personalized
therapeutic regimen design. The use of Bayesian statistical modeling provides an unprecedented opportunity in the field of anti-HIV therapy to understand detailed interaction structures of drug resistant mutations. Multiple Bayesian models equipped with Markov Chain Monte Carlo (MCMC) methods have been recently proposed in this field (Zhang et al. in PNAS 107:1321, 2010 [1]; Zhang et al. in J Proteome Sci Comput Biol 1:2, 2012 [2]; Svicher et al. in Antiviral Res 93(1):86-93, 2012 [3]; Svicher et al. in Antiviral Therapy 16(7):1035-1045, 2011 [4]; Svicher et al. in Antiviral Ther 16(4):A14-A14, 2011 [5]; Svicher et al. in Antiviral Res 93(1):86-93, 2012 [6]; Alteri et al. in Signature mutations in V3 and bridging sheet domain of HIV-1 gp120 HIV-1 are specifically associated with dual tropism and modulate the interaction with CCR5 N-Terminus, 2011 [7]). Probabilistically modeling mutations in the HIV-1 protease or reverse transcriptase (RT) isolated from drug-treated patients provides a powerful statistical procedure that first detects mutation combinations associated with single or multiple-drug resistance, and then infers detailed dependence structures among the interacting mutations in viral proteins (Zhang et al. in PNAS 107:1321, 2010 [1]; Zhang et al. in J Proteome Sci Comput Biol 1:2, 2012 [2]). Combined with molecular dynamics simulations and free energy calculations, Bayesian analysis predictions help to uncover genetic and structural mechanisms in the HIV treatment resistance. Results obtained with such stochastic methods pave the way not only for optimization of the use for existing HIV drugs, but also for the development of the new more efficient antiretroviral medicines. In this chapter we survey current challenges in the bioinformatics of anti-HIV therapy, and outline how recently emerged Bayesian methods can help with the clinical management of HIV-1 infection. We will provide a rigorous review of the Bayesian variable partition model and the recursive model selection procedure based on probability theory and mathematical data analysis techniques while highlighting real applications in HIV and HBV studies including HIV drug resistance (Zhang et al. in PNAS 107:1321, 2010 [1]), cross-resistance (Zhang et al. in J Proteome Sci Comput Biol 1:2, 2012 [2]), HIV coreceptor usage (Svicher et al. in Antiviral Therapy 16(7):1035-1045, 2011 [4]; Svicher et al. in Antiviral Ther 16(4):A14-A14, 2011 [5]; Alteri et al. in Signature mutations in V3 and bridging sheet domain of HIV-1 gp120 HIV-1 are specifically associated with dual tropism and modulate the interaction with CCR5 N-Terminus, 2011 [7]), and occult HBV infection (Svicher et al. in Antiviral Res 93(1):86-93, 2012 [3]; Svicher et al. in Antiviral Ther 16(4):A85-A85, 2011 [6]).

(60) Krentz HB, MacDonald J, Gill MJ. The impact of transfer patients on the local cascade of HIV care continuum. Journal of Acquired Immune Deficiency Syndromes: JAIDS 2015 Feb 1;68(2):236-240

BACKGROUND: The Cascade of Care (COC) visualizes stages of HIV care progression within a population. It is predicated on a local population model and thus may not address the impact on the COC of HIV-experienced individuals diagnosed and cared for elsewhere who move into the area. METHODS: All individuals with a confirmed HIV+ test in Calgary, Canada, between January 1, 2006, and January 1, 2013 were included. Individuals were categorized as "local" if diagnosed within the area, or "transfer" if diagnosed elsewhere. Subgroups were separately placed within the COC and then aggregated. RESULTS: Of 1019 new cases, 47% were transfers. Transfer patients were more likely female (35% vs. 23%; P < 0.01), non-white (61% vs. 46%; P < 0.001), heterosexual (56% vs. 38%; P < 0.001), and have higher CD4
counts (400 vs. 282/mm) with undetectable viremia in 57% [63% on antiretroviral therapy (ART)] at baseline. Engagement was higher at every stage for transfer patients: 94% of transfer vs. 92% of local patients linked to HIV care, 90% vs. 76% (P < 0.001) were retained, 86% vs. 67% (P < 0.001) received ART, and at study’s end, 75% vs. 58% (P < 0.001) had undetectable viremia. When patients were aggregated, linkage increased by 1%, retention by 6%, patient use of ART by 8%, and patients with viral suppression by 7%. CONCLUSIONS: The COC of local and transfer patients differs so significantly that both need to be considered separately in measuring COC, adding a previously under-recognized level of complexity. Use of aggregate COC without considering different levels of engagement could lead to imprecise information for public health initiatives and program metrics.


BACKGROUND: Data on changes in metabolic syndrome (MetS) status in HIV-infected adults on antiretroviral therapy (ART) are limited. METHODS: MetS was assessed at ART initiation and every 48 weeks on ART in ART-naive HIV-infected individuals from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) cohort. MetS, defined using the Adult Treatment Panel III criteria, required at least 3 of the following: elevated fasting glucose, hypertension, elevated waist circumference, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol. Prevalence of MetS and the individual criteria were compared between ART initiation and during follow-up using McNemar test. RESULTS: At ART initiation, 450 (20%) ALLRT participants had MetS. After 96 weeks of ART, 37% of the 411 with MetS at ART initiation and with available data at this time point did not meet the MetS criteria. Among these participants, there was a dramatic decline in the proportion with low HDL (95% versus 26%, P 4 criteria was higher at week 96 compared to at the time of ART initiation (48% versus 40%, P = 0.03); at week 96, the proportion with high triglycerides was greater (87% versus 69%, P < 0.0001) as was the proportion with high glucose (59% versus 42%, P < 0.0001). CONCLUSIONS: One in 5 ART-naive subjects met criteria for MetS at ART initiation. Although more than half of these individuals continued to have MetS after 96 weeks of ART, 37% with MetS at ART initiation no longer met criteria for MetS; this decrease was driven largely by increases in HDL cholesterol.


OBJECTIVES: The objective of the study is to investigate the causes of febrile illness among HIV-infected adults visiting the emergency department (ED) of a designated hospital for HIV care in Taiwan, an area of a low HIV prevalence. METHODS: From January 2004 to December 2012, all febrile HIV-infected adults visiting the ED were retrospectively investigated. Recent CD4 lymphocyte counts
near ED visits and HIV transmission route were designated as major predictors for
the analyses. All variables and clinical information were derived from chart records.
RESULTS: Of the 196 eligible HIV-infected adults, major causes of febrile illness
were lower respiratory tract infections (68, 34.7%), skin and soft tissue infections (31,
15.8%), intra-abdominal infections (22, 11.2%), and urinary tract infections (11,
5.6%). There were 150 pathogens identified. Staphylococcus aureus (51, 34.0%) and
Pneumocystis jirovecii (26, 17.3%) were the major pathogens. In a multivariate
analysis, injection drug use (odds ratio, 15.18; P < .001) and skin and soft tissue
infections (odds ratio, 18.45; P = .001) were independently associated with S aureus
infections, and the proportion of S aureus increased steadily with CD4 lymphocyte
count ( = 0.99; P = .01). Of pneumonic patients with recognized pathogens, P.
jirovecii pneumonia was frequently associated with patients having a CD4
lymphocyte count of less than 100 cells/mm(3) (25/25, 100% vs 16/30, 53.3%; P <
.001). CONCLUSIONS: The causes of febrile illness in HIV-infected adults visiting
the ED varied according to CD4 count and transmission route. Two independent risk
factors, intravenous drug use and skin and soft tissue infections, were associated
with S aureus infections. For HIV-infected adults with lower respiratory tract
infections, a CD4 lymphocyte count of less than 100 cells/mm(3) was a risk factor for
P. jirovecii pneumonia. Copyright © 2014 Elsevier Inc. All rights reserved.

(64) Levy I. HIV-associated neurocognitive disorders: still a hot topic?. Israel

Cytomegalovirus coinfection is associated with an increased risk of severe
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BACKGROUND: Chronic cytomegalovirus (CMV) infection has been associated
with immunosenescence and immunoactivation in the general population. In human
immunodeficiency virus type 1 (HIV-1)-infected people, CMV coinfection, in addition
to residual HIV replication and microbial translocation, has been proposed as a key
factor in sustaining immune activation, even in individuals with a controlled HIV load.
METHODS: Patients from the ICONA Study with at least 1 CMV immunoglobulin G
(IgG) test available without active CMV disease were included in the analysis. AIDS-
defining event or AIDS-related death and severe non-AIDS-defining event or non-
AIDS-related death were taken as clinical progression end points. Independent
predictors of CMV were identified by multivariable logistic regression. Probabilities of
reaching the end points were estimated by survival analyses. RESULTS: A total of
6111 subjects were included, of whom 5119 (83.3%) were CMV IgG positive at
baseline. Patients with CMV IgG positivity at baseline were more likely to develop a
severe non-AIDS-defining event/non-AIDS-related death (adjusted hazard ratio [HR],
1.53 [95% confidence interval {CI}, 1.08-2.16]. In particular, CMV seropositivity was
an independent risk factor for cardiovascular and cerebrovascular diseases
(adjusted HR, 2.27 [95% CI, .97-5.32]). CONCLUSIONS: In our study population,
CMV/HIV coinfection was associated with the risk of severe non-AIDS-defining
events/non-AIDS-related death, especially with cardiovascular and cerebrovascular
events, independently of other prognostic factors. This finding supports a potential
independent role of CMV coinfection in vascular/degenerative organ disorders in
HIV-infected subjects. Copyright © The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.


OBJECTIVE: Data comparing the efficacy and safety of combination therapy with peginterferon plus low-dose ribavirin and peginterferon monotherapy in treatment-naive haemodialysis patients with hepatitis C virus genotype 2 (HCV-2) infection are limited. DESIGN: In this randomised trial, 172 patients received 24 weeks of peginterferon alfa-2a 135 μg/week plus ribavirin 200 mg/day (n=86) or peginterferon alfa-2a 135 μg/week (n=86). The efficacy and safety endpoints were sustained virological response (SVR) rate and adverse event (AE)-related withdrawal rate. RESULTS: Compared with monotherapy, combination therapy had a greater SVR rate (74% vs 44%, relative risk (RR): 1.68 [95% CI 1.29 to 2.20]; p<0.001), and patients receiving combination therapy were more likely to have a haemoglobin level of <8.5 g/dL (70% vs. 8%, risk difference (RD): 62% [95% CI 50% to 73%]; p<0.001) and required a higher dosage [mean: 13,417 vs. 6,667 IU/week, p=0.027] of epoetin beta to manage anaemia than those receiving monotherapy. The AE-related withdrawal rates were 6% and 3% in combination therapy and monotherapy groups, respectively (RD: 2% [95% CI -4% to 9%]). CONCLUSIONS: In treatment-naive haemodialysis patients with HCV-2 infection, combination therapy with peginterferon plus low-dose ribavirin achieved a greater SVR rate than peginterferon monotherapy. Most haemodialysis patients can tolerate combination therapy. TRIAL REGISTRATION NUMBER: ClinicalTrials.gov number, NCT00491244. Copyright Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions.


Hepatitis B virus (HBV) chronic infections remain a considerable health problem worldwide. The standard therapies have demonstrated limited efficacy, side effects or need life-long treatments. Nowadays therapeutic vaccination is a promising option. Recently, we developed a new vaccine formulation called Nasvac, based on the combination of surface and core antigens from HBV. Clinical trials already performed showed good efficacy in virus control. However, the exact mode of action of Nasvac formulation remains unclear. So far the functional impairment of DCs during persistent HBV infection is a controversial issue. On the other hand, it is known that B cells may function as antigen presenting cells (APC) activating T cells. The hepatitis B core antigen contained in Nasvac vaccine is able to bind and activate a high frequency of naive human B cells. In the present study the surface expression...
of activation and exhaustion markers on B cells and the subsequent activation of T cells after in vitro stimulation with Nasvac antigens were evaluated in chronic HBV patients and healthy donors. B- and T-cell phenotype and proliferation were assessed by flow cytometry. Our results indicate that in contrast to exhaustions markers B cell activation markers were increased on both study groups after Nasvac stimulation. A shift toward an activation phenotype was observed for both B and T cells. The present work suggests that B cells could act as efficient APCs for Nasvac antigens in humans, which might suggest the use of activated B cells as immunotherapeutic strategy for chronic hepatitis B. Copyright © 2014 Elsevier Ltd. All rights reserved.

(68) London GM, Mayosi BM, Khati M. **Isolation and characterization of 2'-F-RNA aptamers against whole HIV-1 subtype C envelope pseudovirus**. Biochemical & Biophysical Research Communications 2015 Jan 2;456(1):428-433

Aptamers, which are artificial nucleic acid ligands akin to antibodies in function, represent a new class of molecules that can prevent HIV infection. In this study, we isolated RNA aptamers against whole HIV-1CAP45 enveloped pseudotyped virus, with a view to target surface molecules that facilitate infection, such as the envelope protein, in their native form. HIV-1CAP45 belongs to subtype C viruses endemic in Sub-Saharan Africa and responsible for the majority of the global HIV-1 infections. After nine rounds of the systematic evolution of ligands by exponential enrichment (SELEX) method, we isolated twenty-three aptamer clones that inhibited infection of target cells by HIV-1CAP45 with 50% inhibitory concentration (IC50) values of 0.1-50 nM. Four of these aptamers called CSIR1.1, CSIR1.4, CSIR1.5 and CSIR1.6 bound to gp120 with affinity constant (KD) values between 16.9 and 195 nM and one aptamer called CSIR1.2 bound gp41. Interestingly, one aptamer called CSIR1.3 that did not bind gp120 or gp41 also inhibited infection of the target cells by HIV-1CAP45 with IC50 of less than 5 nM. Taken together, these data show that the aptamers inhibit infection of HIV-1CAP45 by binding to gp120 or gp41, or other viral surface molecules necessary for infection. The results argue in favour of using these aptamers as analytical tools to further probe HIV-1 entry, and their future development as HIV-1 entry inhibitors. Copyright © 2014 Elsevier Inc. All rights reserved.


Hepatitis C virus (HCV) infection causes acute and chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). However, the mechanisms by which HCV causes the diseases are largely unknown. Here, we elucidated the effects of HCV on the invasion and migration of hepatoma cells, with the aim to reveal the mechanism by which HCV infection induces HCC. We initially showed that matrix metalloproteinase-9 (MMP-9) was elevated in the sera of HCV-infected patients, and demonstrated that HCV nonstructural protein 3 (NS3) activated MMP-9 transcription through nuclear factor-kappaB (NF-kappaB) by stimulating translocation of NF-kappaB from cytosol to the nucleus to enhance its binding to MMP-9 promoter. In
addition, cyclooxygenase-2 (COX-2) and extracellular signal-regulated kinase (ERK1/2)/mitogen-activated protein kinase (p38) pathway were involved in HCV-activated MMP-9 expression. Moreover, NS3 enhanced hepatoma cell invasion and migration through MMP-9 and COX-2. Thus, this study provides new insights into the roles of HCV NS3, MMP-9 and COX-2 in regulating cancer cell invasion.

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INTRODUCTION: HIV transmission cluster analyses can inform HIV prevention efforts. We describe the first such assessment for transmission clustering among HIV patients in Chicago. METHODS: We performed transmission cluster analyses using HIV pol sequences from newly diagnosed patients presenting to Chicago's largest HIV clinic between 2008 and 2011. We compared sequences through progressive pairwise alignment, using neighbor joining to construct an unrooted phylogenetic tree. We defined clusters as >2 sequences among which each sequence had at least 1 partner within a genetic distance of 1:16 concurrent with their HIV diagnosis. We had HIV transmission risk data for 54%; 43% identified as men who have sex with men (MSM). Phylogenetic analysis demonstrated 123 patients (13%) grouped into 26 clusters, the largest having 20 members. In multivariable regression, age 1:16 associated with clustering. We did not observe geographic grouping of genetically clustered patients. DISCUSSION: Our results demonstrate high rates of HIV transmission clustering, without local geographic foci, among young black MSM in Chicago. Applied prospectively, phylogenetic analyses could guide prevention efforts and help break the cycle of transmission.


Infection with the human immunodeficiency virus (HIV) causes systemic T cell destruction and reduced cell-mediated immunity that leads to a wide range of opportunistic infections and cancers. Second, it directly damages many tissues - gut, brain, lung - through mononuclear cell infection and activation. Third, through immune activation and effects on endothelia, it can cause more subtle systemic organ damage, such as chronic cardiovascular, hepatic, pulmonary and central nervous system disease. Antiretroviral treatment has enabled HIV-infected persons to live with chronic infection, although with some side-effects and mortality, including reactions due to the immune reconstitution inflammatory syndrome (IRIS). As cohorts of infected people get older, age-related diseases will combine with chronic HIV infection to produce disabilities whose scale is not yet understood. HIV is detectable in tissues by immunohistochemistry when infection loads are high, such as at first presentation. Pathologists should proactively consider HIV disease in routine diagnostic work, so as to identify more HIV-infected patients and enable their optimal management. Copyright © 2014 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.


BACKGROUND: A 2010 New York law requires that patients aged 13-64 years be offered HIV testing in routine medical care settings. Past studies report the clinical outcomes, cost-effectiveness, and budget impact of expanded HIV testing nationally and within clinics but have not examined how state policies affect resource needs and epidemic outcomes. METHODS: A system dynamics model of HIV testing and care was developed, where disease progression and transmission differ by awareness of HIV status, engagement in care, and disease stage. Data sources include HIV surveillance, Medicaid claims, and literature. The model projected how alternate implementation scenarios would change new infections, diagnoses, linkage to care, and living HIV cases over 10 years. RESULTS: Without the law, the model projects declining new infections, newly diagnosed cases, individuals newly linked to care, and fraction of undiagnosed cases (reductions of 62.8%, 59.7%, 54.1%, and 57.8%) and a slight increase in living diagnosed cases and individuals in care (2.2% and 6.1%). The law will further reduce new infections, diagnosed AIDS cases, and the fraction undiagnosed and initially increase and then decrease newly diagnosed cases. Outcomes were consistent across scenarios with different testing offer frequencies and implementation times but differed according to the level of implementation. CONCLUSIONS: A mandatory offer of HIV testing may increase diagnoses and avert infections but will not eliminate the epidemic. Despite declines in new infections, previously diagnosed cases will continue to need access to antiretroviral therapy, highlighting the importance of continued funding for HIV care.


BACKGROUND: The hallmark of HIV infection is progressive but variable rates of systemic and mucosal CD4 depletion, leading to immunodeficiency. The impact of early HIV infection on cervical CD4 T-cell populations in humans remains poorly described. METHODS: We analyzed cytobrush-derived immune cells by flow cytometry and cytokines in cervicovaginal lavage from participants in early HIV (10-fold in early HIV infection and Th1 cells (defined as CCR6CXCR3) were reduced by...
>2-fold. Although CCR6CCR10 cells did not differ in HIV receptor expression, these cells produced higher levels of interferon gamma and interleukin 17. CONCLUSIONS: These data support the model of initial CD4 T-cell depletion followed by overall T-cell influx in response to infection and concomitant increases in immune activation, inflammation, and regulatory markers. These data are among the earliest characterization of the cellular milieu in the female genital tract following male-to-female HIV transmission.


OBJECTIVE: To investigate the diagnostic value of quantitative plasma cytomegalovirus (CMV)-DNA polymerase chain reaction (PCR) for CMV end-organ diseases (CMV-EOD) in patients with HIV-1 infection. DESIGN: Single-center cross-sectional study. METHODS: The study subjects were HIV-1-infected patients with CD4 10,086 IU/mL: 26.1%, 94.1%, 18.8%, 96%; >2946 IU/mL: 56.5%, 86.8%, 18.3%, 97.4%; >959 IU/mL: 60.9%, 78.1%, 12.7%, 97.4%; detectable CMV-DNA (>185 IU/mL): 91.3%, 48.2%, 8.5%, 99.1%; for all CMV-EOD: >10,086 IU/mL: 32.4%, 95.3%, 37.5%, 94.2%; >2946 IU/mL: 54.1%, 88%, 28.2%, 95.6%; >959 IU/mL: 62.2%, 79.5%, 20.9%, 96%; detectable CMV-DNA: 91.9%, 49.5%, 13.7%, 98.6%. CONCLUSIONS: Plasma CMV-DNA PCR has a high diagnostic value for both CMV retinitis and all CMV-EOD in patients with advanced HIV-1 infection. A cutoff value of CMV-DNA >10,086 IU/mL and >2946 IU/mL yields high specificity, whereas undetectable CMV-DNA load (<185 IU/mL) likely rules out CMV-EOD.


BACKGROUND: To elucidate the benefits of successful antiviral therapy in chronic hepatitis C (CHC) patients METHODS: A total of 463 CHC patients who underwent pegylated interferon alfa and ribavirin therapy were classified as sustained virological response (SVR) or non-SVR based on response to antiviral therapy. We investigated disease progression to cirrhosis in non-cirrhotic patients, development of cirrhosis-related complications such as ascites, variceal bleeding, and hepatic encephalopathy in patients with cirrhosis, and development of hepatocellular carcinoma (HCC). RESULTS: Three hundred patients achieved SVR, and 163 were classified into the non-SVR group. The overall SVR rates were 64.8%, and multivariate analysis showed that younger age, non-cirrhosis, HCV genotype 2 or 3, lower HCV RNA level (<800,000 IU/mL), and lower body weight were independent factors associated with SVR (all P < 0.05). During a median follow-up of 36.1 months, non-cirrhotic patients with SVR had significantly lower risk of progression to cirrhosis compared with patients with non-SVR (P < 0.001). Moreover, SVR was related to a reduced risk of HCC development (P = 0.017). CONCLUSIONS: SVR resulted in significantly more favorable long-term outcomes,
such as lower risk of progression to cirrhosis and HCC occurrence compared with non-SVR.


... Antiretroviral therapy initiation is associated with declines in bone mineral density (BMD), which seem greatest with tenofovir disoproxil fumarate (DF)-containing regimens. Data comparing protease inhibitors are limited. This CASTLE substudy compared paired baseline with week 96 BMD in patients initiating tenofovir DF/emtricitabine plus atazanavir/ritonavir (n = 106) vs lopinavir/ritonavir (n = 70). In both groups, week 96 BMD declined significantly in arm, leg, trunk, and total body regions. Atazanavir/ritonavir was associated with smaller 96-week trunk and total body BMD declines compared with lopinavir/ritonavir [multivariate-adjusted least squares mean difference +2.00% (95% confidence interval: 0.52 to 3.45; P = 0.008) and +1.24% (95% confidence interval: 0.13 to 2.35; P = 0.029), respectively]. In addition, low baseline CD4 cell count (<50 cells per microliter) and increasing age were associated with larger declines in BMD.


... BACKGROUND: The outcome of kidney transplantation in human immunodeficiency virus (HIV)-positive patients who receive organs from HIV-negative donors has been reported to be similar to the outcome in HIV-negative recipients. We report the outcomes at 3 to 5 years in HIV-positive patients who received kidneys from HIV-positive deceased donors. METHODS: We conducted a prospective, nonrandomized study of kidney transplantation in HIV-infected patients who had a CD4 T-cell count of 200 per cubic millimeter or higher and an undetectable plasma HIV RNA level. All the patients were receiving antiretroviral therapy (ART). The patients received kidneys from deceased donors who tested positive for HIV with the use of fourth-generation enzyme-linked immunosorbent assay at the time of referral. All the donors either had received no ART previously or had received only first-line ART. RESULTS: From September 2008 through February 2014, a total of 27 HIV-positive patients underwent kidney transplantation. Survivors were followed for a median of 2.4 years. The rate of survival among the patients was 84% at 1 year, 84% at 3 years, and 74% at 5 years. The corresponding rates of graft survival were 93%, 84%, and 84%. (If a patient died with a functioning graft, the calculation was performed as if the graft had survived.) Rejection rates were 8% at 1 year and 22% at 3 years. HIV infection remained well controlled, with undetectable virus in blood after the transplantation. CONCLUSIONS: Kidney transplantation from an HIV-positive donor appears to be an additional treatment option for HIV-infected patients requiring renal-replacement therapy. (Funded by Sanofi South Africa and the Roche Organ Transplantation Research Foundation.).

The treatments for chronic hepatitis B (CHB) are interferon and nucleoside analogues reverse transcriptase (RT) inhibitors. Because both treatments are less than ideal, we conducted to identify novel anti-viral agents for HBV-reverse transcriptase (HBV-RT). We determined the ligand-binding site of the HBV-RT by conducting a homological search of the amino acid sequence and then we also determined not only structural arrangement of the target protein but the target protein-binding site of the ligand using known protein-ligand complexes in registered in the protein data bank (PDB). Finally we simulated binding between the ligand candidates and the HBV-RT and evaluated the degree of binding (in silico screening). PXB cells derived from human-mouse chimeric mouse liver, infected with HBV were administrated with the candidates, and HBVDNA in the culture medium was monitored by realtime qPCR. Among compounds from the AKosSamples database, twelve candidates that can inhibit RT were also identified, two of which seem to have the potential to control HBV replication in vitro. Copyright © 2014 Elsevier Inc. All rights reserved.

(82) Mutimer D. **Ribavirin with interferon for hepatitis C in dialysis patients: efficacious and safe in the right patients in good hands**. Gut 2015 Feb;64(2):190-191


The molecular mechanisms for IL2 gene-specific dysregulation during chronic human immunodeficiency virus type 1 (HIV-1) infection are unknown. Here, we investigated the role of DNA methylation in suppressing interleukin 2 (IL-2) expression in memory CD4(+) T cells during chronic HIV-1 infection. We observed that CpG sites in the IL2 promoter of CD4(+) T cells were fully methylated in naive CD4(+) T cells and significantly demethylated in the memory populations. Interestingly, we found that the memory cells that had a terminally differentiated phenotype and expressed CD57 had increased IL2 promoter methylation relative to less differentiated memory cells in healthy individuals. Importantly, early effector memory subsets from HIV-1-infected subjects expressed high levels of CD57 and were highly methylated at the IL2 locus. Furthermore, the increased CD57 expression on memory CD4(+) T cells was inversely correlated with IL-2 production. These data suggest that DNA methylation at the IL2 locus in CD4(+) T cells is coupled to immunosenescence and plays a critical role in the broad dysfunction that occurs in polyclonal T cells during HIV-1 infection. Copyright © The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
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BACKGROUND: Human immunodeficiency virus (HIV) is a significant risk factor for pulmonary arterial hypertension. There is a significant added risk for maternal mortality when superimposed on the physiologic changes of pregnancy. CASE: A 37-year-old HIV-positive woman underwent caesarean delivery at 27 weeks of gestation for chorioamnionitis and malpresentation after premature rupture of membranes. Postpartum, she was diagnosed with HIV-associated pulmonary arterial hypertension, which was managed successfully with sildenafil and ambrisentan.

CONCLUSION: Pulmonary arterial hypertension associated with HIV is a life-threatening complication that may occur in pregnant women with HIV. The rarity of the condition, overlapping with symptoms commonly seen in pregnancy, and its broad differential diagnosis may confound the diagnosis. Prompt recognition and therapy are required to optimize clinical outcomes.


BACKGROUND: Traditional cardiovascular disease risk factors (CVDRFs) increase the risk of acute myocardial infarction (AMI) among HIV-infected (HIV+) participants. We assessed the association between HIV and incident AMI within CVDRF strata.

METHODS: Cohort-81,322 participants (33% HIV+) without prevalent CVD from the Veterans Aging Cohort Study Virtual Cohort (prospective study of HIV+ and matched HIV- veterans) participated in this study. Veterans were followed from first clinical encounter on/after April 1, 2003, until AMI/death/last follow-up date (December 31, 2009). Predictors-HIV, CVDRFs (total cholesterol, cholesterol-lowering agents, blood pressure, blood pressure medication, smoking, diabetes) used to create 6 mutually exclusive profiles: all CVDRFs optimal, 1+ nonoptimal CVDRFs, 1+ elevated CVDRFs, and 1, 2, 3+ major CVDRFs. Outcome-Incident AMI [defined using enzyme, electrocardiogram (EKG) clinical data, 410 inpatient ICD-9 (Medicare), and/or death certificates]. Statistics-Cox models adjusted for demographics, comorbidity, and substance use. RESULTS: Of note, 858 AMIs (42% HIV+) occurred over 5.9 years (median). Prevalence of optimal cardiac health was <2%. Optimal CVDRF profile was associated with the lowest adjusted AMI rates. Compared with HIV- veterans, AMI rates among HIV+ veterans with similar CVDRF profiles were higher. Compared with HIV- veterans without major CVDRFs, HIV+ veterans without major CVDRFs had a 2-fold increased risk of AMI (HR: 2.0; 95% confidence interval: 1.0 to 3.9; P = 0.044). CONCLUSIONS: The prevalence of optimal cardiac health is low in this cohort. Among those without major CVDRFs, HIV+ veterans have twice the AMI risk. Compared with HIV- veterans with high
CVDRF burden, AMI rates were still higher in HIV+ veterans. Preventing/reducing CVDRF burden may reduce excess AMI risk among HIV+ people.


Induction of a strong hepatitis C virus (HCV)-specific immune response plays a key role in control and clearance of the virus. A polytope (PT) DNA vaccine containing B- and T-cell epitopes could be a promising vaccination strategy against HCV, but its efficacy needs to be improved. The N-terminal domain of heat shock protein gp96 (NT(gp96)) has been shown to be a potent adjuvant for enhancing immunity. We constructed a PT DNA vaccine encoding four HCV immunodominant cytotoxic T lymphocyte epitopes (two HLA-A2- and two H2-D(d)-specific motifs) from the Core, E2, NS3 and NS5B antigens in addition to a T-helper CD4+ epitope from NS3 and a B-cell epitope from E2. The NT(gp96) was fused to the C- or N-terminal end of the PT DNA (PT-NT(gp96) or NT(gp96)-PT), and their potency was compared. Cellular and humoral immune responses against the expressed peptides were evaluated in CB6F1 mice. Our results showed that immunization of mice with PT DNA vaccine fused to NT(gp96) induced significantly stronger T-cell and antibody responses than PT DNA alone. Furthermore, the adjuvant activity of NT(gp96) was more efficient in the induction of immune responses when fused to the C-terminal end of the HCV DNA polytope. In conclusion, the NT(gp96) improved the efficacy of the DNA vaccine, and this immunomodulatory effect was dependent on the position of the fusion.


Antibodies with modest neutralizing activity and narrow breadth are commonly elicited in HIV-1. Here, we evaluated the complementary and synergetic activities of a set of monoclonal antibodies (MAb) isolated from a single patient, directed to V3, CD4 binding site (CD4bs), and CD4 induced (CD4i) epitopes. Despite low somatic hypermutation percentages in the variable regions, these MAbs covered viral strains from subtypes B, C, A and CRF01_AE and transmitted/founder viruses in terms of binding, neutralizing and antibody-dependent cell-mediated cytotoxicity (ADCC) activities. In addition, a combination of the anti-V3 and CD4bs MAbs showed a synergetic effect over the neutralization of HIV-1JR-FL. A humoral response from a single patient covered a wide range of viruses by complementary and synergetic activities of antibodies with different specificities. Inducing a set of narrow neutralizing antibodies, easier to induce than the broadly neutralizing antibodies, could be a strategy for developing an effective vaccine against HIV-1. Copyright © 2014 Elsevier Inc. All rights reserved.

or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): a randomised, double-blind, non-inferiority phase 3 trial. The Lancet Infectious Diseases 2015 Jan;15(1):27-35

BACKGROUND: We did a phase 3 study in previous non-responders with chronic hepatitis C virus (HCV) genotype 1 infection and compensated liver disease that related to the standard of care for these patients at the time this study was initiated. We investigated whether simeprevir is non-inferior in terms of efficacy to telaprevir, each in combination with peginterferon alfa-2a and ribavirin. METHODS: We did this randomised, double-blind, phase 3 trial at 169 investigational sites in 24 countries. We enrolled adults (>18 years) with chronic HCV genotype 1 infection, compensated liver disease, and plasma HCV RNA higher than 10 000 IU/mL who were null or partial responders during at least one previous course of peginterferon alfa-2a and ribavirin treatment. We randomly assigned (1:1) patients (stratified by HCV genotype 1 subtype [1a plus other/1b] and previous treatment response [partial or null]) to receive simeprevir (150 mg once a day) plus telaprevir placebo (three times a day 7-9 h apart) or telaprevir (750 mg three times a day) plus simeprevir placebo (once a day) in combination with peginterferon alfa-2a and ribavirin for 12 weeks followed by 36 weeks of peginterferon alfa-2a and ribavirin alone. The primary efficacy endpoint was sustained virological response 12 weeks after end of treatment (SVR12) in the intention-to-treat and the per-protocol population. We compared groups with the Cochran-Mantel-Haenszel test. We established a non-inferiority margin of 12%. Adverse events were reported descriptively. This trial is registered with ClinicalTrials.gov, number NCT01485991. FINDINGS: Patient screening began on Jan 19, 2012, and the last visit was on April 7, 2014. We included 763 patients (472 previous null responders [62%]). Simeprevir and peginterferon alfa-2a and ribavirin was non-inferior to telaprevir and peginterferon alfa-2a and ribavirin for SVR12 (54% [203/379] vs 55% [210/384]; difference -11%, 95% CI -78 to 55; p=00007). SVR12 was achieved in 70% (101/145) versus 68% (100/146) of previous partial responders and 44% (102/234) versus 46% (110/238) of previous null responders with simeprevir and peginterferon alfa-2a and ribavirin and telaprevir and peginterferon alfa-2a and ribavirin treatment, respectively. We recorded differences between treatment groups in simeprevir or telaprevir-related adverse events (69% [261/379] in the simeprevir group vs 86% [330/384] in the telaprevir group), serious adverse events (2% [8/379] vs 9% [33/384]), and adverse events leading to simeprevir or telaprevir discontinuation (2% [7/379] vs 8% [32/384]). INTERPRETATION: Simeprevir once a day with peginterferon alfa-2a and ribavirin was well tolerated in HCV genotype 1-infected previous non-responders and was non-inferior to telaprevir, thus providing an alternative treatment in areas of the world where all-oral HCV regimens are not available or accessible. FUNDING: Janssen. Copyright © 2015 Elsevier Ltd. All rights reserved.


Chronic hepatitis B virus (HBV) infection remains the number one risk factor for hepatocellular carcinoma (HCC), accounting for more than 600,000 deaths/year. Despite highly effective antiviral treatment options, chronic hepatitis B (CHB), subsequent end-stage liver disease and HCC development remain a major challenge worldwide. In CHB, liver damage is mainly caused by the influx of immune cells and destruction of infected hepatocytes, causing necro-inflammation. Treatment with nucleoside/nucleotide analogues can effectively suppress HBV replication in patients with CHB and thus decrease the risk for HCC development. Nevertheless, the risk of HCC in treated patients showing sufficient suppression of HBV DNA replication is significantly higher than in patients with inactive CHB, regardless of the presence of baseline liver cirrhosis, suggesting direct, long-lasting, predisposing effects of HBV. Direct oncogenic effects of HBV include integration in the host genome, leading to deletions, cis/trans-activation, translocations, the production of fusion transcripts and generalized genomic instability, as well as pleiotropic effects of viral transcripts (HBsAg and HBx). Analysis of these viral factors in active surveillance may allow early identification of high-risk patients, and their integration into a molecular classification of HCC subtypes might help in the development of novel therapeutic approaches.


: This prospective, open-label nonrandomized controlled trial evaluated the efficacy, safety, and pharmacokinetics of substituting nevirapine/emtricitabine/tenofovir for rilpivirine/emtricitabine/tenofovir in 50 suppressed HIV-1 switchers. One hundred thirty-nine nonswitchers remained on nevirapine as controls. Week 12 HIV-1 RNA was <50 copies per milliliter in 92.0% of switchers and was <50 copies per milliliter at week 24 in 88.0% of switchers and 90.6% of nonswitchers (difference 2.6%, 95% confidence interval: -7.6% to 12.8%). Week 3 geometric mean nevirapine concentration was undetectable and week 1 geometric mean rilpivirine concentration (0.083 mg/L) was comparable with phase 3 trial (P = 0.747). Substituting nevirapine for rilpivirine resulted in ongoing virological suppression and did not have clinically relevant pharmacokinetic effects by cytochrome P450 interactions.

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OBJECTIVES: The invasive nature of biopsy alongside issues with categorical
staging and sampling error has driven research into noninvasive biomarkers for the assessment of liver fibrosis in order to stratify and personalize treatment of patients with liver disease. Here, we sought to determine whether a metabonomic approach could be used to identify signatures reflective of the dynamic, pathological metabolic perturbations associated with fibrosis in chronic hepatitis C (CHC) patients.

METHODS: Plasma nuclear magnetic resonance (NMR) spectral profiles were generated for two independent cohorts of CHC patients and healthy controls (n=50 original and n=63 validation). Spectral data were analyzed and significant discriminant biomarkers associated with fibrosis (as graded by enhanced liver fibrosis (ELF) and METAVIR scores) identified using orthogonal projection to latent structures (O-PLS).

RESULTS: Increased severity of fibrosis was associated with higher tyrosine, phenylalanine, methionine, citrate and, very-low-density lipoprotein (vLDL) and lower creatine, low-density lipoprotein (LDL), phosphatidylcholine, and N-Acetyl-alpha1-acid-glycoprotein. Although area under the receiver operator characteristic curve analysis revealed a high predictive performance for classification based on METAVIR-derived models, <40% of identified biomarkers were validated in the second cohort. In the ELF-derived models, however, over 80% of the biomarkers were validated.

CONCLUSIONS: Our findings suggest that modeling against a continuous ELF-derived score of fibrosis provides a more robust assessment of the metabolic changes associated with fibrosis than modeling against the categorical METAVIR score. Plasma metabolic phenotypes reflective of CHC-induced fibrosis primarily define alterations in amino-acid and lipid metabolism, and hence identify mechanistically relevant pathways for further investigation as therapeutic targets.


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Cytomegalovirus (CMV) remains a significant cause of morbidity after allogeneic hematopoietic stem cell transplantation (HSCT). Clinical risk varies according to a number of factors, including recipient/donor CMV serostatus. Current dogma suggests risk is greatest in seropositive recipient (R+)/seronegative donor (D-) transplants and is exacerbated by T-cell depletion. We hypothesized that in the setting of reduced-intensity T-cell-depleted conditioning, recipient-derived CMV-specific T cells escaping deletion may contribute significantly to CMV-specific immunity and might therefore also influence chimerism status. We evaluated 105 recipients of alemtuzumab-based reduced-intensity HSCT and collated details on CMV infection episodes and T-cell chimerism. We used CMV-specific HLA multimers to enumerate CMV-specific T-cell numbers and select cells to assess chimerism status in a subset of R+/D- and R+/seropositive donor patients. We show that in R+/D- patients, CMV-specific T cells are exclusively of recipient origin, can protect against recurrent CMV infections, and significantly influence the chimerism status
toward recipients. The major findings were replicated in a separate validation cohort. T-cell depletion in the R+/D- setting may actually, therefore, foster more rapid reconstitution of protective antiviral immunity by reducing graft-vs-host directed alloreactivity and the associated elimination of the recipient T-cell compartment. Finally, conversion to donor chimerism after donor lymphocytes is associated with clinically occult transition to donor-derived immunity. Copyright © 2015 by The American Society of Hematology.


Malaria-specific immune responses are altered in HIV/malaria-coinfected individuals and are associated with higher parasite burdens and more severe clinical disease. Monocyte/macrophage phagocytosis is a major mechanism of malaria parasite clearance. We hypothesized that phagocytosis of malaria-parasitized erythrocytes is impaired in coinfected individuals and could contribute to the increased parasite burdens observed. We show that nonopsonic phagocytosis of Plasmodium falciparum parasitized erythrocytes is impaired in monocytes isolated from HIV-infected individuals. The observed defects in phagocytic capacity were rescued after 6 months of antiretroviral therapy, demonstrating the importance of HIV treatment and immune reconstitution in the context of coinfection.


Over the past three decades, perinatal HIV infection in the United States has evolved from a fatal disease to a manageable chronic illness. As the majority of youth with perinatal HIV infection age into adolescence and adulthood, management of this stigmatizing, transmittable disease in the backdrop of a cadre of environmental stressors presents challenges beyond those of other chronic illnesses. The neurologic and neuropsychological consequences of this neurotropic virus have important implications for the successful navigation of responsibilities related to increasingly independent living of this aging population. This article will review the neurologic and neuropsychological consequences of perinatal HIV infection and concomitant factors in the era of highly active antiretroviral therapy and will provide an overview of the neuropathology, pathogenesis, neuroimaging findings, and treatment of perinatal HIV infection, as well as recommendations for service provision and future research.


Liver cancers are one of the deadliest known malignancies which are increasingly becoming a major public health problem in both developed and developing countries.

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Overwhelming evidence suggests a strong role of infection with hepatitis B and C virus (HBV and HCV), alcohol abuse, as well as metabolic diseases such as obesity and diabetes either individually or synergistically to cause or exacerbate the development of liver cancers. Although numerous etiologic mechanisms for liver cancer development have been advanced and well characterized, the lack of definite curative treatments means that gaps in knowledge still exist in identifying key molecular mechanisms and pathways in the pathophysiology of liver cancers. Given the limited success with current therapies and preventive strategies against liver cancer, there is an urgent need to identify new therapeutic options for patients. Targeting HCV and or alcohol-induced signal transduction, or virus-host protein interactions may offer novel therapies for liver cancer. This review summarizes current knowledge on the mechanistic development of liver cancer associated with HCV infection and alcohol abuse as well as highlights potential novel therapeutic strategies.


BACKGROUND AND OBJECTIVE: Precore (PC) variant (G1896A) and basal core promoter (BCP) variant (A1762T/G1764A) of HBV are associated with risk of hepatocellular carcinoma in HBV carriers. However, little is known about their impact on the adverse outcomes of hepatitis B e antigen (HBeAg)-negative hepatitis and liver cirrhosis. METHODS: 251 spontaneous HBeAg seroconverters who had genotype B or C infection and received a long-term follow-up were enrolled. PC and BCP mutants were determined qualitatively and quantitatively to correlate with these adverse outcomes. The findings were validated by an independent case-control study, which included 184 patients with biopsy-proven liver fibrosis stages. RESULTS: In the longitudinal cohort study, BCP mutant and possibly PC wild type were associated with cirrhosis development, but not HBeAg-negative hepatitis. Multivariable analysis showed that only BCP mutant was an independent risk factor for cirrhosis development. Using quantitative analysis of BCP mutant, a higher proportion of BCP mutant, defined as a continuous variable, a dichotomous variable or an ordinal variable, was associated with a higher risk of cirrhosis. If we chose 45% of BCP mutant as the cut-off, the risk of cirrhosis was higher in patients with BCP mutant >45% compared to <45% in the longitudinal cohort; this finding was validated by the case-control study (adjusted OR: 2.81, 95% CI 1.40 to 5.67). CONCLUSIONS: A higher proportion of BCP mutant increases the risk of liver cirrhosis development in HBV carriers with genotype B or C infection. Copyright Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions.


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Leptin is a hormone secreted by adipocytes that regulates energy metabolism via peripheral action on glucose synthesis and utilization as well as through central regulation of food intake. Patients with decreased amounts of fat in their adipose tissue (lipoatrophy) will have low leptin levels, and hypoleptinemic states have been associated with a variety of metabolic dysfunctions. Pronounced complications of insulin resistance, dyslipidemia and fatty liver are observed in patients suffering from congenital or acquired generalized lipodystrophy while somewhat less pronounced abnormalities are associated with human immunodeficiency virus (HIV) and the use of highly active antiretroviral therapy, the so-called HIV-associated lipodystrophy. Previous uncontrolled open-label studies have demonstrated that physiological doses of leptin repletion have corrected many of the metabolic derangements observed in subjects with rare fat maldistribution syndromes such as generalized lipodystrophy. In the much more commonly encountered HIV-associated lipodystrophy, leptin replacement has been shown to decrease central fat mass and to improve insulin sensitivity, dyslipidemia, and glucose levels. The United States Food and Drug Administration has recently granted approval for recombinant leptin therapy for congenital and acquired generalized lipodystrophy, however large, well-designed, placebo-controlled studies are needed to assess long-term efficacy, safety and adverse effects of leptin replacement. In this review, we present the role of leptin in the metabolic complications of congenital and acquired lipodystrophy and discuss current and emerging clinical therapeutic uses of leptin in humans with lipodystrophy. Copyright © 2015 Elsevier Inc. All rights reserved.


UNLABELLED: Hepatitis B envelope antigen (HBeAg) seroconversion represents an endpoint of treatment of chronic hepatitis B virus (HBV) infections. We have studied whether levels of serum HBV RNA during polymerase inhibitor treatment might be helpful for predicting HBeAg seroconversion. HBV RNA levels were determined in serial serum samples from 62 patients with chronic HBV infection (50 HBeAg positive). Patients received antiviral treatment for a mean duration of 30 +/- 15 (range, 4-64) months. A new rapid amplification of complimentary DNA-ends-based real-time polymerase chain reaction was established for quantitative analysis of polyadenylated full-length (fl) and truncated (tr) HBV RNA. HBV RNA, HBV DNA, and hepatitis B surface antigen (HBsAg) levels as well as presence of HBeAg and hepatitis B envelope antibody were measured at baseline, month 3, month 6, and subsequent time points. Fifteen patients who achieved HBeAg seroconversion after a mean duration of 19 +/- 14 (range, 3-56) months of antiviral treatment showed a significantly stronger decline in mean HBV flRNA and trRNA levels from baseline to month 3 of 1.0 +/- 1.4 (range, -1.6-3.4) and 2.1 +/- 1.4 (range, 0-3.9) and to month 6 of 1.8 +/- 1.4 (range, 0-4.6) and 3.1 +/- 1.7 (range, 0-5.1) log10 copies/mL, respectively, in comparison to 35 HBeAg-positive patients without HBeAg seroconversion (P < 0.001 for months 3 and 6). A similar decline in HBV RNA levels was observed in HBeAg-negative patients. The decline of HBV RNA levels at months 3 and 6 of treatment was to be the strongest predictor of HBeAg
seroconversion, when compared to levels of HBV DNA, HBsAg, alanine aminotransferase, and HBV genotype, age, and sex. CONCLUSION: Serum HBV RNA levels may serve as a novel tool for prediction of serological response during polymerase inhibitor treatment in HBeAg-positive patients. Copyright © 2014 by the American Association for the Study of Liver Diseases.


OBJECTIVE: Reliable tools to predict long-term outcome among patients with well compensated advanced liver disease due to chronic HCV infection are lacking. DESIGN: Risk scores for mortality and for cirrhosis-related complications were constructed with Cox regression analysis in a derivation cohort and evaluated in a validation cohort, both including patients with chronic HCV infection and advanced fibrosis. RESULTS: In the derivation cohort, 100/405 patients died during a median 8.1 (IQR 5.7-11.1) years of follow-up. Multivariate Cox analyses showed age (HR=1.06, 95% CI 1.04 to 1.09, p<0.001), the observed 5-year mortality rates in the derivation cohort and validation cohort were 0.9% (95% CI 0.0 to 2.7) and 2.6% (95% CI 0.0 to 6.1), 8.1% (95% CI 1.8 to 14.4) and 8.0% (95% CI 1.3 to 14.7), 21.8% (95% CI 13.2 to 30.4) and 20.9% (95% CI 13.6 to 28.1), respectively (C statistic in validation cohort=0.76, 95% CI 0.69 to 0.83). The risk score for cirrhosis-related complications also incorporated HCV genotype (C statistic=0.80, 95% CI 0.76 to 0.83 in the derivation cohort; and 0.74, 95% CI 0.68 to 0.79 in the validation cohort). CONCLUSIONS: Prognosis of patients with chronic HCV infection and compensated advanced liver disease can be accurately assessed with risk scores including readily available objective clinical parameters. Copyright Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions.


BACKGROUND: The HIV care continuum has been used to show the proportion of persons living with HIV/AIDS (PWHA) who are engaged in each stage of HIV care. We present 1 care continuum for persons newly diagnosed with HIV and 1 for PWHA using New York City HIV surveillance registry data. METHODS: Persons newly diagnosed with HIV in 2011 or PWHA as of December 31, 2011, were included. We constructed each continuum for persons engaged at each stage of HIV care and calculated the proportion achieving each step as both dependent on or independent of preceding steps. RESULTS: Of the 3408 newly diagnosed persons, 67% had timely linkage to care (1 visit), 70% retained in care (>2 visits >3 months apart), and 52% suppressed at their last visit; losses were highest from retention to suppression.
When measured independently, suppression increased to 58%. **CONCLUSIONS:** A minority of persons newly diagnosed with HIV and a narrow majority of PWHA achieved viral suppression and all intermediate care-related steps. Outcomes measured independently of previous care-related steps were higher, particularly for newly diagnosed persons. To improve outcomes among persons with HIV and reduce transmissibility, clinical and public health efforts should focus on linkage to care among newly diagnosed persons and viral suppression among PWHA.


We examined the role of human cytokines in the natural course of hepatitis B surface Ag (HBsAg) seroconversion in chronic hepatitis B virus (HBV) infection. The clinical course of spontaneous HBsAg seroconversion was assessed in 296 chronically HBV-infected patients. Single nucleotide polymorphisms (SNPs) in IL-1beta, IL-2, IL-4, IL-10, IL-12beta, IL-13, IL-27, and IFN- genes were examined in 296 chronically HBV-infected patients and another 193 HBV recoverers. The HBsAg a determinant sequence of chronically HBV-infected subjects with and without HBsAg seroconversion was also analyzed. The start of the immune-clearance phase (serum alanine aminotransferase levels > 30 IU/l) before the age of 48 mo and hepatitis B e Ag (HBeAg) seroconversion before the age of 10 y predicted spontaneous HBsAg seroconversion in chronically HBV-infected patients (odds ratios 17.7 and 5.0; p < 0.001 and p < 0.002, respectively). The A-allele of IL-10 SNP rs1800872 was associated with higher IL-10 serum levels, and the G-allele of IL-12beta SNP rs3212217 was associated with sustained high serum IL-12p70 levels during the immune-clearance phase. Both were predictors of spontaneous HBsAg seroconversion and HBV recovery (odds ratios 4.0 and 26.3; p = 0.002 and p < 0.001, respectively). Spontaneous HBsAg seroconversion was not related to sex, HBV genotype, or HBsAg a determinant mutation. The start of immune-clearance phase, age at HBeAg seroconversion, and serum IL-10 and IL-12 levels are associated with the course of the immune-clearance phase in chronic HBV infection, and are predictive of spontaneous HBsAg seroconversion and HBV recovery.

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**BACKGROUND:** To investigate the clinicopathologic characteristics of patients with both hepatitis B virus-surface antigen and hepatitis C virus antibody negative hepatocellular carcinoma (non-B non-C HCC [NBNC-HCC]) and examine the impact of occult hepatitis B virus infection (OBI) on patients' survival. **METHODS:** All patients with OBI were identified from a database of patients with NBNC-HCC who underwent surgical resection between January 1, 2006, and December 31, 2008. Their clinicopathologic and survival characteristics were compared with NBNC-HCC patients without OBI. **RESULTS:** Out of the 86 NBNC-HCC patients, 59 patients (68.6%) with OBI. A higher prevalence of hepatitis B core antigen positive rate, low
platelet count, portal hypertension, and liver cirrhosis were observed in NBNC-HCC patients with OBI. The 1- and 3-y recurrence free survival rates were 66% and 25% in OBI group and 89% and 70% in the no OBI group, respectively (P < 0.001). The 1-, 3-, and 5-y overall survival rates were 86%, 55%, and 51% in OBI group and 93%, 85%, and 66% in no OBI group, respectively (P = 0.112). Multivariate analysis revealed that OBI (hazard ratio [HR] = 2.122; 95% confidence interval [CI], 1.086-4.149; P = 0.028), liver cirrhosis (HR = 2.411; 95% CI, 1.337-4.345; P = 0.003), and vascular invasion (HR = 5.858; 95% CI, 2.799-12.261; P < 0.001) were independent poor prognostic factors for recurrence free survival of patients with NBNC-HCC.

CONCLUSIONS: NBNC-HCC patients with OBI had a poorer prognosis. OBI can be a useful predictor for recurrence in patients with NBNC-HCC after surgery. 

(112) Xia Q, Ning Z, Torian LV. A run-in period is needed in randomized controlled trials of directly observed antiretroviral therapy for HIV infection. Journal of Acquired Immune Deficiency Syndromes: JAIDS 2015 Feb 1;68(2):e20-3


UNLABELLED: The aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on the four factors (Fibrosis 4 index; FIB-4) are the two most widely studied noninvasive tools for assessing liver fibrosis. Our aims were to systematically review the performance of APRI and FIB-4 in hepatitis B virus (HBV) infection in adult patients and compare their advantages and disadvantages. We examined the diagnostic accuracy of APRI and FIB-4 for significant fibrosis, advanced fibrosis, and cirrhosis based on their sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating characteristic curve (AUROC). Heterogeneity was explored using metaregression. Our systemic review and meta-analysis included 16 articles of APRI only, 21 articles of APRI and FIB-4 and two articles of FIB-4 for detecting different levels of liver fibrosis. With an APRI threshold of 0.5, 1.0, and 1.5, the sensitivity and specificity values were 70.0% and 60.0%, 50.0% and 83.0%, and 36.9% and 92.5% for significant fibrosis, advanced fibrosis, and cirrhosis, respectively. With an FIB-4 threshold of 1.45 and 3.25, the sensitivity and specificity values were 65.4% and 73.6% and 16.2% and 95.2% for significant fibrosis. The summary AUROC values using APRI and FIB-4 for the diagnosis of significant fibrosis, advanced fibrosis, and cirrhosis were 0.7407 (95% confidence interval [CI]: 0.7033-0.7781) and 0.7844 (95% CI: 0.7450-0.8238; Z=1.59, P=0.06), 0.7347 (95% CI: 0.6790-0.7904) and 0.8165 (95% CI: 0.7707-0.8623; Z=2.01, P=0.02), and 0.7268 (95% CI: 0.6578-0.7958) and 0.8448 (95% CI: 0.7742-0.9154; Z=2.34, P=0.01), respectively. CONCLUSIONS: Our meta-analysis suggests that APRI and FIB-4 can identify hepatitis B-related fibrosis with a moderate sensitivity and accuracy. Copyright © 2014 by the American Association for the Study of Liver Diseases.

BACKGROUND: Human T-lymphotropic virus type 1 (HTLV-1) can cause chronic spinal cord inflammation, known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Since CD4(+)CCR4(+) T cells are the main HTLV-1 reservoir, we evaluated the defucosylated humanized anti-CCR4 antibody mogamulizumab as a treatment for HAM/TSP. METHODS: We assessed the effects of mogamulizumab on peripheral blood mononuclear cells from 11 patients with HAM/TSP. We also studied how CD8(+) T cells, namely CD8(+) CCR4(+) T cells and cytotoxic T lymphocytes, are involved in HTLV-1 infection and HAM/TSP pathogenesis and how they would be affected by mogamulizumab. RESULTS: Mogamulizumab effectively reduced the HTLV-1 proviral load (56.4% mean reduction at a minimum effective concentration of 0.01 microg/mL), spontaneous proliferation, and production of proinflammatory cytokines, including interferon (IFN-). Like CD4(+)CCR4(+) T cells, CD8(+)CCR4(+) T cells from patients with HAM/TSP exhibited high proviral loads and spontaneous IFN- production, unlike their CCR4(-) counterparts. CD8(+)CCR4(+) T cells from patients with HAM/TSP contained more IFN--expressing cells and fewer interleukin 4-expressing cells than those from healthy donors. Notably, Tax-specific cytotoxic T lymphocytes that may help control the HTLV-1 infection were overwhelmingly CCR4(-). CONCLUSIONS: We determined that CD8(+)CCR4(+) T cells and CD4(+)CCR4(+) T cells are prime therapeutic targets for treating HAM/TSP and propose mogamulizumab as a new treatment. Copyright © The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.


UNLABELLED: Historically, clinical trials of regimens to treat chronic infection with hepatitis C virus (HCV) have used, as their primary efficacy endpoint, a sustained virological response (SVR)-defined as HCV RNA levels below a designated threshold of quantification-24 weeks after the end of treatment (SVR24). More recently, regulatory authorities have begun to accept SVR at 12 weeks post-treatment (SVR12) as a valid efficacy endpoint because of its high rate of concordance with SVR24. However, the concordance between SVR12 and SVR24 has not been systematically assessed with new regimens of recently approved direct-acting antiviral agents. The aim of this study was to assess the concordance between SVR at various post-treatment time points in phase III clinical trials of sofosbuvir (SOF)-containing regimens. We conducted a retrospective analysis of five trials enrolling 863 patients infected with HCV genotypes 1-6. The concordance between SVR at 4 weeks post-treatment (SVR4) and SVR12, and between SVR12 and SVR24, were determined, as well as positive predictive values (PPVs) and negative predictive values (NPVs). Overall, 779 of 796 patients (98.0%) with an
SVR4 also achieved an SVR12, making the PPV of SVR4 for SVR12 98% and the NPV 100%. Of the 779 patients with an SVR12, 777 (99.7%) also achieved an SVR24, making the PPV of SVR12 for SVR24 >99% and the NPV 100%. Of patients who relapsed post-therapy, 77.6% did so within 4 weeks of completing therapy.

CONCLUSION: Data from phase III studies demonstrate that with SOF-based regimens, with or without interferon, SVR12 and SVR24 correlate closely. Thus, SVR12 can be used effectively to determine "cure" rates in trials and in clinical practice.

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BACKGROUND: A flow-based treatment device using riboflavin and ultraviolet (UV) light was developed to inactivate viruses in fresh-frozen plasma (FFP). The objective of this study was to evaluate the in vitro effectiveness of virus inactivation and changes in protein quality in FFP treated with this device.

STUDY DESIGN AND METHODS: FFP-contaminating viruses were treated with riboflavin and UV light using a one-pass linear flow device. The infectivity of viruses was measured using established biologic assays. Real-time polymerase chain reaction (PCR) was performed to detect damage to viral nucleotides after treatment. Treated plasma was analyzed using standard coagulation assays. RESULTS: FFP treated at the UV dose of 3.6J/cm(2) (J) exhibited a mean reduction of virus titer of more than 4 logs. The effectiveness increased significantly at higher doses. Real-time PCR showed that the cycle threshold values for both complete inactivation and virus recultivation were higher than that of the untreated sample. At doses of 3.6, 5.4, and 7.2J, the protein recovery rates were 60.2+/-8.6, 46.6+/-9.4, and 28.0+/-1.0% for fibrinogen; 67.0+/-3.1, 57.3+/-8.0, and 49.2+/-3.8% for Factor VIII; 93.6+/-2.8, 89.6+/-6.1, and 86.5+/-5.3% for antithrombin-III; and 72.1+/-5.6, 59.8+/-14.2, and 49.2+/-8.4% for Protein C, respectively.

CONCLUSION: The effectiveness of virus inactivation was enhanced, but total activity of plasma factors was reduced, in a UV dose-dependent manner.

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Progressive quantitative and qualitative decline of CD4(+) T cell responses is one hallmark of HIV-1 infection and likely depends on several factors, including a possible contribution by the HIV-1 envelope glycoprotein gp120, which binds with high affinity to the CD4 receptor. Besides virion-associated and cell-expressed gp120, considerable amounts of soluble gp120 are found in plasma or lymphoid tissue, predominantly in the form of gp120-anti-gp120 immune complexes (ICs). Because the functional consequences of gp120 binding to CD4(+) T cells are controversially discussed, we investigated how gp120 affects TCR-mediated activation of human CD4(+) T cells by agonistic anti-CD3 mAb or by HLA class II-
presented peptide Ags. We show that the spatial orientation of gp120-CD4 receptor binding relative to the site of TCR engagement differentially affects TCR signaling efficiency and hence CD4(+) T cell activation. Whereas spatially and temporally linked CD4 and TCR triggering at a defined site promotes CD4(+) T cell activation by exceeding local thresholds for signaling propagation, CD4 receptor engagement by gp120-containing ICs all around the CD4(+) T cell undermine its capacity in supporting proximal TCR signaling. In vitro, gp120 ICs are efficiently captured by CD4(+) T cells and thereby render them hyporesponsive to TCR stimulation. Consistent with these in vitro results we show that CD4(+) T cells isolated from HIV(+) individuals are covered with ICs, which at least partially contain gp120, and suggest that IC binding to CD4 receptors might contribute to the progressive decline of CD4(+) T cell function during HIV-1 infection. Copyright © 2015 by The American Association of Immunologists, Inc.