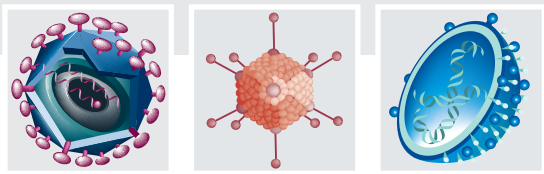


Bulletin Board

HIV screening and treatment, a natural combination? Cost–effectiveness study announces results

A central question in the struggle against HIV concerns the best way in which to allocate limited resources in terms of disease detection, treatment and prevention. A recent meta-analysis study on the cost–effectiveness of broader HIV screening policies and/or expanded access to antiretroviral therapy (ART) has returned results indicating that, while both of these options would be cost effective, a combination of the two would reap even more benefits. As Elisa Long (Yale University, CT, USA), first author of the paper detailing the study puts it, "Multiple studies from independent research groups have corroborated the finding that HIV screening is cost effective; our study delineates the additional benefit of augmenting HIV screening with improved ART access" [Long E, Pers. Comm.].

In the USA, it is estimated that 21% of individuals who are infected with HIV are unaware of their status, a situation that is extremely conducive to further spread of the disease, and which currently limits the usefulness of further scaling-up of treatment – if an individual is unaware that they are infected, they will not seek out treatment even if it is freely available.

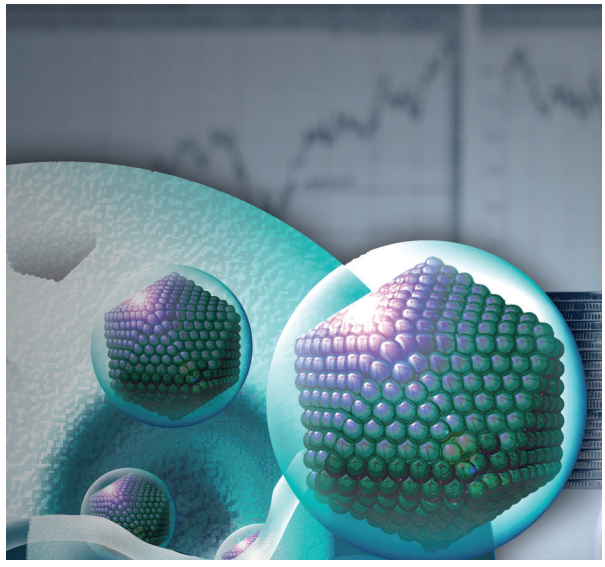
On the other hand, while widespread HIV screening alone would no doubt be useful in helping to control the spread of the disease, a lack of sufficient easily available ART to go with this screening would cause the opportunity to ensure that individuals diagnosed with HIV achieve virological control (with the accompanying reduction in risk of transmission) as soon as possible to be missed.

This synergy of screening and treatment is the central message that can be taken from this meta-analysis. As Long puts it: "A key finding from our study is that programs emphasizing the simultaneous scale-up of HIV screening and antiretroviral treatment are more effective and cost-effective than exclusively focusing on either intervention independently".

Aside from these policy decisions, there are behavioral aspects to consider as well. Previous experience with HIV screening has demonstrated that it is one thing to collect samples and analyze them, but quite another to make sure that the individual concerned returns to receive the results of the test. Encouragingly for those seeking to minimize time and resources wasted in this manner, Long adds that "…use of a rapid HIV test to improve receipt of test results [has] been shown to be both effective and cost-effective".

Although there are potential problems with a greatly increased HIV screening program, there is confidence that these can be overcome. Logistical issues associated with testing so many people would be minimized, as "The implementation … would be incrementally phased in over time".

Moving on to discuss the potential consequences of the currently-estimated 21% of existing HIV-positive individuals unaware of their status receiving this information, Long commented that, "Available evidence suggests that an effective counseling program accompanying HIV screening can reduce risk behaviors modestly", and that "there has been no precedent for increased behavioral disinhibition following HIV screening".



in the news...

Sources: Stanford Medical School press release, 20 December 2010 (Ruthann Richter); Long EF, Brandeau ML, Owens DK: The cost–effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the United States. *Ann. Int. Med.* 153(12), 778–789 (2010).

Laboratory contamination controversy over possible viral cause for chronic fatigue syndrome

The controversy over a potential viral cause for chronic fatigue syndrome (CFS) has heated up considerably in recent months, with failures to replicate the findings of the study that started the debate, suggestions that the original findings were due to laboratory contamination and rebuttals of this via press releases. With both sides of the argument releasing attention-grabbing headlines, it is hard to say who is correct on this issue.

Chronic fatigue syndrome is an enigmatic condition that has gone by a wide variety of names in different times and places, such as 'myalgic encephalomyelitis', or 'chronic fatigue immune dysfunction syndrome' among many others. Without a widely accepted diagnostic test, cause, mechanism or treatment, the lack of precise nomenclature is at the same time both unsurprising and also not the foremost issue with regard to this condition.

The recent controversy relating CFS to a possible viral cause began in 2009, with the publication of a study by Vincent Lombardi *et al*., which reported the detection of xenotropic murine leukemia virus (XMRV) in the blood of individuals suffering from CFS. This announcement triggered a significant response from both the scientific community and from CFS patient organizations, eager for more information.

> "Humans do not make antibody responses to mouse DNA sequences from contaminated lab experiments."

Prevailing opinion subsequently swayed back and forth following the publication, first, of several follow-up studies carried out to investigate this finding that failed to reproduce the results of the original, and, subsequently, of a study that claimed to have detected retrovirus *gag* gene sequences similar to those of XMRV in 87% of blood samples taken from CFS patients and only 7% of those taken from healthy volunteers. The most recent chapter in terms of published studies was the publication of four studies in late 2010 that, combined, gave the overall impression that laboratory contamination as a potential source for the original results connecting XMRV to CFS could not be ruled out. Summarized by a quote from Greg Towers (University College London, UK), "XMRV is not the cause of CFS", this twist to the tale received a great deal of media coverage, which may have prompted the 1 January press release from Annette Whittemore, President of the Whittemore Peterson Institute (MN, USA), refuting this conclusion with: "Humans do not make antibody responses to mouse DNA sequences from contaminated lab experiments".

While it appears to be true that the latest set of studies simply point out possibilities for contamination rather than conclusively demonstrating it, the genetic similarity observed across the XMRV strains found – an unusual result given the instability of the average retrovirus – does seem to raise valid questions concerning their likely source.

As the focus shifts away from the publication of results and towards press releases, quotes and newspaper coverage, it is likely that published studies, with their inherent time lag, will be outpaced by speculation, at least until sufficiently convincing evidence is obtained to settle the issue one way or another.

Sources: Lombardi VC, Ruscetti FW, Das Gupta J *et al.* Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* 326(5952), 585–589 (2009); Wellcome Trust press release, 6 January 2011: Chronic fatigue syndrome not caused by XMRV virus, study shows: www.wellcome.ac.uk/News/Media-office/Press-releases/2011/WTX064078.htm

Priority Paper Alerts

Chi CN, Bach A, Engstrom A *et al.* Biophysical characterization of the complex between human papillomavirus E6 protein and synapse associated protein 97. *J. Biol. Chem.* 286(5), 3597–3606 (2010).

Human papillomavirus (HPV) can sometimes persistently infect an individual for years, potentially leading to cervical cancer. This study examined the interaction between the HPV E6 protein and three PDZ domains of the human tumor-suppressor protein SAP97, believed to be potential binding sites. It was found that all three sites were able to bind E6, both individually and simultaneously, although the affinity of E6 protein differed among different strains of HPV. Given that the hydrodynamic volume of the PDZ domains did not appear to differ before and after binding the E6, it was theorized (and later supported by kinetic experiments) that a binding-associated conformational change resulted in compaction. In addition, the use of NMR uncovered an E6–PDZ interaction. This discovery may prove helpful in limiting the ability of HPV to inhibit tumor-suppressor proteins and encourage progress towards a cure.

Bendavid E, Grant P, Talbot A, Owens DK, Zolopa A. Cost–effectiveness of antiretroviral regimens in the World Health Organization's treatment guidelines: a South African analysis. *AIDS* 25(2) 211–220 (2011).

Although the WHO has recently released new guidelines for antiretroviral treatment, questions remain as to their applicability in some cases. This study attempted to simulate the cost–effectiveness of these new guidelines in a model comparing four antiretroviral regimens recommended in the latest WHO guidelines with a fifth, the current most commonly used regimen. An almost 12-month difference in quality-adjusted life expectancy was predicted between the various first-line regimens, with one regime (stavudine/lamivudine/nevirapine) being both more costly and less effective. Aside from this, there was the expected association between treatment cost and effectiveness. Overall, it was found that, of the four WHO-recommended regimens, only three should be considered for use, while stavudine/lamivudine/nevirapine should only be considered in special circumstances.

Immune system response to oncogenic virus uncovered

Epstein–Barr virus (EBV) is a common oncogenic herpesvirus that has been implicated in a wide variety of autoimmune diseases, but that appears to be largely asymptomatic in the vast majority of the estimated 95% of the global adult population it infects.

> "When this oncogenic stress response is activated, it keeps the virus in check, and now we know why."

Despite possessing the ability to immortalize B cells, potentially creating indefinitely growing lymphoblastoid cell lines and therefore cancer, this series of events occurs only rarely, an observation that may have resulted in the recent investigation, led by Micah Luftig (Duke University School of Medicine, NC, USA), into the mechanisms by which virus-mediated cell transformation is suppressed by the immune system. As the study paper put it, "The immortalization efficiency is very low, suggesting that an innate tumor-suppressor mechanism is operative".

Adding to this, Luftig explained that, "We proposed that the cell was sensing that the virus is trying to take over. When this oncogenic stress response is activated, it keeps the virus in check, and now we know why".

The mechanism in question is a DNA damage response, triggered by latent infection with EBV, that greatly inhibits B-cell transformation in the early stages of infection. Should the virus gain the upper hand at any point, however, it can cause the production of the viral latent oncoprotein EBNA3C, which greatly reduces the DNA damage response, allowing B-cell immortalization and, potentially, cancer.

This discovery may have implications for the prevention and therapy of virus-related cancer, especially since it appears that the pathway is general rather than specific to EBV. As Luftig commented, "This finding can be extended to the general case of any oncogene being activated that might start the process of tumor formation".

Sources: Nikitin PA, Yan CM, Forte E *et al.*: An ATM/Chk2-mediated DNA damage-responsive signaling pathway suppresses Epstein–Barr virus transformation of primary human B cells. *Cell Host Microbe* 8(6), 510–522 (2010); Duke University Medical Center press release: Scientists decode secrets of a very common virus that can cause cancer: www.dukehealth.org/health_library/news/scientists-decode-secrets-of-a-very-common-virus-that-can-cause-cancer

New discovery suggests herpesvirus immune modulation occurs at earlier stage

It is well known that many pathogenic viruses are capable of modulating host immune response in order to allow them to persist, but the precise details of this modulation are often unclear. In the case of γ-herpesvirus-68, an *in vivo* mouse model of the human Epstein–Barr virus, a multinational team primarily based in the Walter and Eliza Hall Institute of Medical Research (Victoria, Australia) and Cambridge University (UK) has discovered that the viral gene *K3* mediates interference with dendritic cell antigen presentation, inhibiting immune response to the virus at one of the earliest stages.

Dendritic cells are known for being key to the early detection of infection, processing antigens from pathogens they encounter and presenting them to other immune cells in order to encourage an immune response, and so this inhibition of their activity may well go a long way towards explaining the chronic, persistent infection that Epstein–Barr and associated viruses are known for.

> "If we want to make an effective vaccine, we need to look at these early escape points used by the virus as the first target for trying to generate a more efficient immune response."

This discovery may lead to a rethink of vaccine development strategies – if viral immune modulation is achieved so quickly, countermeasures that take effect after this stage may well be of limited usefulness in preventing chronic infection. As Gabrielle Belz, senior author of the study, explained; "If we want to make an effective vaccine, we need to look at these early escape points used by the virus as the first target for trying to generate a more efficient immune response".

Sources: Mount AM, Masson F, Kupresanin F, Smith CM, May JS, van Rooijen N, Stevenson PG, Belz GT: Interference with dendritic cell populations limits early antigen presentation in chronic -herpesvirus-68 infection. *J. Immunol.* 185(6), 3669–3676 DOI: 10.4049/jimmunol.1001079 (2010); Walter and Eliza Hall Institute of Medical Research press release, 5 January 2011: Viral evasion gene reveals new targets for eliminating chronic infections: www.wehi.edu.au/site/latest_news/viral_evasion_gene_reveals_new_targets_for_eliminating_chronic_infections

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of virology. If you have newsworthy information, please contact: Jacob McCarthy, Commissioning Editor, *Future Virology*; Future Medicine Ltd, Unitec House, 2 Albert Place, London N3 1QB, UK Tel.: +44 (0)20 8371 6090; Fax: +44 (0)20 8343 2313; j.mccarthy@futuremedicine.com