

HIV This Week: what scientific journals said

Welcome to the thirty-seventh issue of ***HIV This Week***! In this issue, we cover **immunology** (infected at birth but healthy in adolescence - immune systems fight back but how?; could long term antiretroviral treatment succeed in depleting HIV's reservoirs?; avoiding the intercurrent infections which could top up HIV's reservoirs), **treatment - immune reconstitution inflammatory syndrome**: fighting back too fast creates an inflammatory storm; which tuberculosis patients are more likely to get IRIS - immune reconstitution inflammatory syndrome?), **migration and mobility** (mobility moves foreign policy; encouragingly low HIV prevalence among conflict-affected and displaced people in 7 sub-Saharan African countries - but still much to be done); **men who have sex with men and methamphetamine use** (providers need to ask to know), **sexually transmitted infections** (bacterial vaginosis: what would it mean if Herpes simplex virus type-2 (HSV-2) facilitates its development?), **prevention of mother-to-child-transmission** (no doubt about evidence of efficacy - implementation is the real issue now), **surveillance** (tailoring second-generation HIV surveillance in Romania to 'know your epidemic'), and **basic science** (stopping the third major HIV enzyme - integrase; molecular umbrellas: a promising new door opens in microbicide development to prevent both HIV and HSV).

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1. Immunology

Ofori-Mante JA, Kaul A, Rigaud M, Fidelia A, Rochford G, Krasinski K, Chandwani S, Borkowsky W. Natural history of HIV infected pediatric long-term or slow progressor population after the first decade of life. *Pediatr Infect Dis J* 2007 Mar;26(3):217-20.

Perinatally infected long-term non-progressors/slow progressors represent a select group of individuals. There is very limited information on this group of children beyond the first decade of life. A group of HIV-infected long-term non-progressor/slow progressor children was studied. Ofori-Mante and colleagues enrolled 20 HIV-infected adolescents who were

receiving no or minimal therapy (defined as single or dual nucleoside therapy) before the age of 10 years and who had maintained CD4 counts above 25% for the first decade of life. The authors analyzed immunologic and virologic characteristics. Thymic receptor excision circles (TREC) were measured on stored frozen peripheral blood mononuclear cells. CD4 count, viral load and other pertinent information including race and age were obtained from individual medical records. The results revealed that nine of the 20 patients recruited were noted to have developed falling CD4 counts at or around puberty, whereas the other 11 remained stable. There was no difference in TREC values or HIV RNA values before or after puberty between the 2 groups of patients. Those who remained stable, in terms of maintaining CD4 T cells as a group had falling viral loads with age. Those whose CD4 values declined after puberty had viral loads that did not decrease with age. The authors conclude that a select group of patients who never received HAART during their first decade of life will continue to maintain good CD4 associated with declining HIV RNA values. Thymic output is not predictive of those that don't maintain CD4 T cells. **Editors' note: How do the immune defences, in this select group of adolescents infected at birth, work to maintain CD4 count levels and produce falling viral loads with age? Answering this question could take us a long way along the path to understanding HIV immunology - and, for that matter, immunology in general.**

Chun TW, Justement JS, Moir S, Hallahan CW, Maenza J, Mullins JI, Collier AC, Corey L, Fauci AS. Decay of the HIV Reservoir in Patients Receiving Antiretroviral Therapy for Extended Periods: Implications for Eradication of Virus. *J Infect Dis* 2007 Jun 15;195(12):1762-4.

The persistence of latently infected resting CD4(+) T cells has been clearly demonstrated in human immunodeficiency virus (HIV)-infected individuals receiving effective antiviral therapy. However, estimates of the half-life of this viral reservoir have been quite divergent. Chun and colleagues demonstrate clear evidence for decay of this HIV reservoir in patients who initiated antiviral therapy early in infection. The half-life of this latent viral reservoir was estimated to be 4.6 months. It is projected that it will take up to 7.7 years of continuous therapy to completely eliminate latently infected resting CD4(+) T cells in infected individuals who initiate antiviral therapy early in HIV infection. **Editors' note: The idea that early treatment could eventually eliminate latently infected CD4 cells is not new but remains to be proven. In the meantime, long term commitment both by individuals to adhere to treatment and by governments and development partners to ensure sustained access to antiretroviral treatment programmes is essential.**

Jones LE, Perelson AS. Transient Viremia, Plasma Viral Load, and Reservoir Replenishment in HIV-Infected Patients on Antiretroviral Therapy. *J Acquir Immune Defic Syndr* 2007 Aug 15; 45(5):483-93

When antiretroviral therapy (ART) is administered for long periods to HIV-1-infected patients, most achieve viral loads that are « undetectable » by standard assay methods (ie, HIV-1 RNA <50 copies/mL). Despite sustaining viral loads lower than the level of detection, a number of patients experience unexplained episodes of transient viremia or viral « blips. » Jones and Perelson propose that transient activation of the immune system by infectious agents may explain these episodes of viremia. Using 2 different mathematical models, one in which blips arise because of target cell activation and subsequent infection and another in which latent cell activation generates blips, the authors establish a nonlinear (power law) relationship between blip amplitude and viral load (under ART) that suggest blips should be

of lower amplitude, and thus harder to detect, as increasingly potent therapy is used. This effect can be more profound than is predicted by simply lowering the baseline viral load from which blips originate. Finally, the authors suggest that sporadic immune activation may elevate the level of chronically infected cells and replenish viral reservoirs, including the latent cell reservoir, providing a mechanism for recurrent viral blips and low levels of viremia under ART. **Editors' note: Intercurrent infections such as colds, flu, and herpes simplex and other sexually transmitted infections in all people tend to activate the immune system transiently to mount a defence. In people living with HIV this immune activation leads to transient HIV viraemia which may replenish viral reservoirs. If the goal is to deplete HIV's reservoirs, then where possible, people living with HIV should take steps to prevent other infections (hand washing, flu shots, safer sex and rapid treatment of sexually transmitted infections) which may replenish the reservoirs.**

2. Treatment - IRIS (immune reconstitution inflammatory syndrome)

Murdoch DM, Venter WD, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. *AIDS Res Ther* 2007 May 8;4:9.

The immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients initiating antiretroviral therapy (ART) results from restored immunity to specific infectious or non-infectious antigens. A paradoxical clinical worsening of a known condition or the appearance of a new condition after initiating therapy characterizes the syndrome. Potential mechanisms for the syndrome include a partial recovery of the immune system or exuberant host immunological responses to antigenic stimuli. The overall incidence of IRIS is unknown, but is dependent on the population studied and its underlying opportunistic infectious burden. The infectious pathogens most frequently implicated in the syndrome are mycobacteria, varicella zoster, herpes viruses, and cytomegalovirus (CMV). No single treatment option exists and depends on the underlying infectious agent and its clinical presentation. Prospective cohort studies addressing the optimal screening and treatment of opportunistic infections in patients eligible for ART are currently being conducted. These studies will provide evidence for the development of treatment guidelines in order to reduce the burden of IRIS. Murdoch and colleagues review the available literature on the pathogenesis and epidemiology of IRIS, and present treatment options for the more common infectious manifestations of this diverse syndrome and for manifestations associated with a high morbidity. **Editors' note: When antiretroviral treatment is initiated, patients with an unrecognized underlying infection may develop an immune reconstitution inflammatory syndrome as their immune systems rev up to face an unwelcome guest that has been hanging around. Identifying these infections and treating them specifically is important but guidelines are needed on the sequencing of this treatment vis-à-vis antiretroviral therapy initiation and relevant monitoring for early detection of inflammatory problems.**

Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS* 2007 Jan 30;21(3):335-41.

Lawn and colleagues' objective was to determine the burden and impact of immune reconstitution disease (IRD) associated with tuberculosis (TB) among patients initiating

antiretroviral treatment (ART) in sub-Saharan Africa. The authors used a retrospective analysis of a study cohort enrolled over 3 years within a community-based ART service in South Africa. Patients receiving treatment for TB at the time ART was initiated (n = 160) were studied. Cases of TB-associated IRD during the first 4 months of ART were ascertained. Results showed that the median baseline CD4 cell count was 68 cells/microl [interquartile range (IQR), 29-133 cells/microl) and ART was initiated after a median of 105 days (IQR, 61-164 days) from TB diagnosis. Although IRD was diagnosed in just 12% (n = 19) of patients overall, IRD developed in 32% (n = 12) of those who started ART within 2 months of TB diagnosis. Pulmonary involvement was observed in 84% (n = 16) and intra-abdominal manifestations were also common (37%). Overall, 4% (n = 7) of the cohort required secondary level health-care for IRD and two (1%) patients died. In multivariate analysis, risk of IRD was strongly associated with early ART initiation and low baseline CD4 cell count. Of patients with CD4 counts < 50 cells/microl, the proportions who developed IRD following initiation of ART within 0-30, 31-60, 61-90, 91-120 and > 120 days of TB diagnosis were 100%, 33%, 14%, 7% and 0%, respectively. The authors conclude that the risk of TB-associated IRD in this setting is very high for those with low baseline CD4 cell counts initiating ART early in the course of anti-tuberculosis treatment. However, most cases were self-limiting; overall secondary health-care utilization and mortality risk from IRD were low.

Editors' note: In this study, immune reconstitution inflammatory syndrome (IRIS) developed in a third of tuberculosis patients who started antiretroviral treatment within 2 months of TB diagnosis. The lower the CD4 count at antiretroviral treatment initiation the higher the risk of IRIS. The real dilemma for such patients and their physicians is how long to wait before starting antiretroviral treatment. This study suggests at least a 90 day wait or longer but more specific studies are ongoing now to determine the ideal length.

3. Migration and mobility

Macpherson DW, Gushulak BD, Macdonald L. Health and foreign policy: influences of migration and population mobility. *Bull World Health Organ* 2007 Mar;85(3):200-6.

International interest in the relationship between globalization and health is growing, and this relationship is increasingly figuring in foreign policy discussions. Although many globalizing processes are known to affect health, migration stands out as an integral part of globalization, and links between migration and health are well documented. Numerous historical interconnections exist between population mobility and global public health, but since the 1990s new attention to emerging and re-emerging infectious diseases has promoted discussion of this topic. The containment of global disease threats is a major concern, and significant international efforts have received funding to fight infectious diseases such as malaria, tuberculosis and HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome). Migration and population mobility play a role in each of these public health challenges. The growing interest in population mobility's health-related influences is giving rise to new foreign policy initiatives to address the international determinants of health within the context of migration. As a result, meeting health challenges through international cooperation and collaboration has now become an important foreign policy component in many countries. However, although some national and regional projects address health and migration, an integrated and globally focused approach is lacking. As migration and population mobility are increasingly important determinants of health, these issues will

require greater policy attention at the multilateral level. **Editors' note: HIV has helped stimulate discussions of the links between migration/mobility and health risks. Economics underpins mobility, both in terms of having to move, as in labour migration, and in terms of being able to move, as in tourism. Mobility may be associated with increased HIV risk if it creates situations of sexual decision-making divorced from familiar social contexts and norms.**

Spiegel PB, Bennedsen AR, Claass J, Bruns L, Patterson N, Yiweza D, Schilperoord M. Prevalence of HIV infection in conflict-affected and displaced people in seven sub-Saharan African countries: a systematic review. *Lancet* 2007 Jun 30;369(9580):2187-95.

Violence and rape are believed to fuel the HIV epidemic in countries affected by conflict. Spiegel and colleagues compared HIV prevalence in populations directly affected by conflict with that in those not directly affected and in refugees versus the nearest surrounding host communities in sub-Saharan African countries. Seven countries affected by conflict (Democratic Republic of Congo, southern Sudan, Rwanda, Uganda, Sierra Leone, Somalia, and Burundi) were chosen since HIV prevalence surveys within the past 5 years had been done and data, including original antenatal-care sentinel surveillance data, were available. The authors did a systematic and comprehensive literature search using Medline and Embase. Only articles and reports that contained original data for prevalence of HIV infection were included. All survey reports were independently evaluated by two epidemiologists to assess internationally accepted guidelines for HIV sentinel surveillance and population-based surveys. Whenever possible, data from the nearest antenatal care and host country sentinel site of the neighbouring countries were presented. 95% CIs were provided when available. Of the 295 articles that met our search criteria, 88 had original prevalence data and 65 had data from the seven selected countries. Data from these countries did not show an increase in prevalence of HIV infection during periods of conflict, irrespective of prevalence when conflict began. Prevalence in urban areas affected by conflict decreased in Burundi, Rwanda, and Uganda at similar rates to urban areas unaffected by conflict in their respective countries. Prevalence in conflict-affected rural areas remained low and fairly stable in these countries. Of the 12 sets of refugee camps, nine had a lower prevalence of HIV infection, two a similar prevalence, and one a higher prevalence than their respective host communities. Despite wide-scale rape in many countries, there are no data to show that rape increased prevalence of HIV infection at the population level. The authors have shown that there is a need for mechanisms to provide time-sensitive information on the effect of conflict on incidence of HIV infection, since they found insufficient data to support the assertions that conflict, forced displacement, and wide-scale rape increase prevalence or that refugees spread HIV infection in host communities. **Editors' note: It is often assumed that HIV prevalence increases in times of conflict, due to rape, transactional sex and changed sexual norms. This review found no evidence of increasing HIV prevalence in seven countries affected by conflict and no evidence of HIV spread from refugee communities to surrounding communities. Although HIV incidence would be a better indicator since HIV prevalence may be affected by mortality in conflict zones, these findings are nonetheless encouraging. However, gender-based violence, including sexual assault, in conflict zones as in peaceful settings, is a human rights violation and zero tolerance of such behaviour remains a key strategy for HIV prevention.**

4. Men who have sex with men and Methamphetamine use

Shoptaw S, Reback CJ. Methamphetamine use and infectious disease-related behaviors in men who have sex with men: implications for interventions. *Addiction* 2007;102 Suppl 1:130-5.

Shoptaw and Reback aimed to review the current evidence regarding the prevalence of methamphetamine use among men who have sex with men (MSM) and to evaluate the factors that contribute to methamphetamine use and potential for sexual transmission of HIV and other infectious diseases. The authors used data based reports to address (1) epidemiology of methamphetamine use in MSM; (2) methamphetamine use and risk behaviours for sexually transmitted infections; and (3) interventions. Their findings showed that methamphetamine use is highly prevalent in MSM. Strong associations between methamphetamine use and HIV-related sexual transmission behaviours are noted across studies of MSM and correspond to increased incidence for HIV and syphilis compared to MSM who do not use the drug. Behavioural treatments produce sustained reductions in methamphetamine use and concomitant sexual risk behaviours among methamphetamine-dependent MSM. In conclusion, brief screening of methamphetamine use for MSM who seek physical, mental health and substance abuse services is recommended. Behavioural interventions that address methamphetamine use may range from brief interventions to intensive out-patient treatments. **Editors' note: If you don't ask, you'll never know. Methamphetamine use can increase the likelihood of sexual risk-taking and therefore of sexually transmitted infections and of HIV acquisition and transmission. Behavioural treatments can work to reduce risk but can't even be offered if providers don't become comfortable asking about drug use and sexual behaviour patterns.**

5. Sexually transmitted infections

Nagot N, Ouedraogo A, Defer MC, Vallo R, Mayaud P, Van de Perre P. Association between bacterial vaginosis and Herpes simplex virus type-2 (HSV-2) infection: implications for HIV acquisition studies. *Sex Transm Infect* 2007 Aug; 83(5):365-8

Bacterial vaginosis (BV) and Herpes simplex virus type-2 (HSV-2) have been linked to an increased risk of HIV-1 acquisition. Recent research suggests an association between BV and HSV-2 acquisition, but the converse has not been investigated. Nagot and colleagues examined the determinants of BV occurrence in a cohort of female sex workers in Burkina Faso. Participants were followed every 3 months for diagnosis of genital infections and report of sexual behaviours. Factors associated with BV occurrence were assessed using Generalised Estimating Equations (GEE) models. The authors enrolled 273 women (mean age, 28 years) and conducted 812 follow-up visits (mean 2.93 visit per woman). Baseline seroprevalence of HIV-1, HSV-2 and recent syphilis were 31.5%, 70.1% and 0.4%, respectively, while baseline prevalence of BV, *Trichomonas vaginalis* (TV) and *Candida albicans* were 20.5%, 3.3% and 2.5%, respectively. In multivariable analysis, HSV-2 (relative risk [RR]=1.73, 95% confidence interval [CI]:1.12-2.65), HIV-1 (RR=1.76, 95%CI:1.30-2.40), TV (RR=1.5, 95%CI:1.0-2.3), and having >3 sexual partners in the preceding week (RR=2.2, 95%CI:1.1-4.6) were independently associated with BV, while hormonal contraception showed a protective effect (RR=0.11, 95%CI:0.02-0.70). The authors conclude that HSV-2 infection was associated with BV occurrence in this population. Since HSV-2 is strongly linked to HIV-1 acquisition, studies assessing the cofactor effect of BV on HIV acquisition should control for the presence of HSV-2. Further studies are required to investigate the relative effect of asymptomatic HSV-2 shedding and/or genital ulcerations on BV occurrence. **Editors' note: Bacterial vaginosis is not considered to be a sexually transmitted infection per se but**

rather an imbalance in the vaginal flora. This imbalance, with an increase in vaginal pH making the vagina less acidic and more alkaline, may be the result of HSV-2 infection. If this is proven to be true then HSV suppressive therapy could improve vaginal ecology in more than one way.

6. *Prevention of mother-to-child-transmission*

Suksomboon N, Poolsup N, Ket-Aim S. Systematic review of the efficacy of antiretroviral therapies for reducing the risk of mother-to-child transmission of HIV infection. *J Clin Pharm Ther* 2007 Jun;32:293-311.

Suksomboon and colleagues' objective was to evaluate the efficacy of antiretroviral therapies in reducing the risk of mother-to-child transmission of HIV infection. The authors used a systematic review and meta-analysis of randomized controlled trials. Clinical trials of anti-retrovirals were identified through electronic searches (MEDLINE, EMBASE, BIOSIS, EBM review and the Cochrane Library) up until November 2006. Historical searches of reference lists of relevant randomized controlled trials, and systematic and narrative reviews were also undertaken. Studies were included if they were (i) randomized controlled trials of any antiretroviral therapy aimed at decreasing the risk of mother-to-child transmission of HIV infection, (ii) reporting outcomes in terms of HIV infection in infant, infant death, stillbirth, premature delivery, or low birth weight. The data were extracted by a single investigator and checked by a second investigator. Disagreements were resolved through discussion or a third investigator. The efficacy was estimated using relative risk (RR), risk difference (RD) and number needed to treat (NNT) together with 95% confidence intervals. Results: Fifteen trials were included in the systematic review. Based on five placebo-controlled trials, a zidovudine regimen reduced the risk of mother-to-child transmission by 43% (95% CI:29-55%). The incidence of low birth weight seems to be decreased with zidovudine (pooled RR 0.75, 95% CI: 0.57-0.99). The efficacy of short-short course of zidovudine was comparable with that of the long-short course. Nevirapine monotherapy given to mothers and babies as a single dose reduced the risk of vertical transmission compared with an intra-partum and post-partum regimen of zidovudine (RR 0.60, 95% CI: 0.41-0.87). Zidovudine plus lamivudine was effective in reducing the risk of maternal-child transmission of HIV (RR 0.63, 95% CI: 0.45-0.90). Adding zidovudine to single-dose nevirapine in babies was no more effective than nevirapine alone (pooled RR 0.88, 95% CI: 0.47-1.63), nor was there any significant difference between zidovudine plus lamivudine and nevirapine. In mothers who were treated with standard antiretroviral therapy, no additional benefit was observed with the addition of a single dose of nevirapine in mothers and newborns. In addition, for mothers who received zidovudine prophylaxis, a two-dose intra-partum/newborn nevirapine reduced the risk of HIV infection and death of babies by 68% (95% CI: 39-83%) and 80% (95% CI: 10-95%), respectively, when compared with placebo. In conclusion, the available evidence suggests that zidovudine alone or in combination with lamivudine and nevirapine monotherapy is effective for the prevention of mother-to-child transmission of HIV. They may also be beneficial in reducing the risk of infant death. Different antiretroviral regimens appear to be comparably effective in reducing HIV transmission from mothers to babies. In mothers already receiving zidovudine prophylaxis, adding a single dose of nevirapine to mothers during labour and giving the same drug to infants may further decrease the risk of vertical transmission and infant death. **Editors' note: This review found single dose nevirapine to be more effective than intra- and post-partum zidovudine but adding two-dose intra partum/newborn nevirapine to**

existing zidovudine prophylaxis reduced the risk of infant infection by 68%. At this point the issue is less which regimen than any regimen — coverage levels for prevention of mother-to-child transmission remain unconscionably low in many low-and middle-income countries.

7. Surveillance

Lejars M, Pitigoi D, Teleman M, Nicolaiciuc D, Reintjes R. Implementing a second-generation HIV surveillance system in Romania: Experiences and challenges. *Wien Klin Wochenschr* 2007;119(7-8):242-247.

Romania is a low prevalence country for HIV. Nevertheless, a special epidemiological situation is evolving because of the high percentage of children who were infected by nosocomial transmission between 1986 and 1991 and the consequent increasing number of sexually transmitted cases in adults, in addition to new cases among injecting drug users. In this particular context and with regard to Romania's accession to EU membership, second-generation surveillance (SGS) systems were to be implemented. Following a SWOT analysis of the existing surveillance system, a National conference, monthly working groups and a workshop for training were organized with concerned people from central level and from six pilot districts. Specialists in epidemiology, infectious diseases, dermato-venerology and health promotion were involved in the process of developing the survey methodologies, which were based on standard protocols. Methods of testing and legal and ethical issues were discussed, especially for illegal or stigmatized behaviours. Based on the specific HIV epidemiology of each district and also for practical reasons, the surveys developed and implemented were: serological and behavioural surveillance at dermato-venerology clinics in two of the selected districts, serological surveillance among patients aged 15-24 admitted to general hospitals in four districts, and behavioural surveillance among high school pupils aged 15-19 in five districts. While implementing SGS, financial and human resource constraints encountered in the development and implementation of the surveys at each location need to be taken into account. One of the most important lessons learnt during this project was the importance of teamwork and co-operation between the epidemiologists and clinicians involved in HIV surveillance. The lessons learned in Romania could be valuable for many regions in Europe. **Editors' note: Low HIV prevalence countries face a "know your epidemic" challenge which calls for tailoring second generation surveillance strategies. Romania's approach included a national conference, working groups, and training workshops. Involving members of populations at higher risk of HIV exposure in programme design, implementation and monitoring will be key to ensuring not only that human rights are respected but also that appropriate strategies for reaching out to marginalised populations are designed and implemented.**

8. Basic science

Nair V, Chi G. HIV integrase inhibitors as therapeutic agents in AIDS. *Rev Med Virol* 2007 Jul-Aug; 17(4):277-95

HIV-1 integrase is a protein of Mr 32 000 encoded at the 3'-end of the pol gene. Integration of HIV DNA into the host cell chromosomal DNA apparently occurs by a carefully defined sequence of DNA tailoring (3'-processing (3'P)) and coupling (integration) reactions. Integration of HIV DNA into human DNA represents the biochemical completion of the invasion of the human cell (e.g., T-cell) by HIV. Unlike major successes seen in the development of clinically approved anti-HIV agents against HIV reverse transcriptase and

HIV protease, there are no FDA-approved anti-HIV drugs in clinical use where the mechanism of action is inhibition of HIV integrase. This review summarises some key advances in the area of integrase inhibitors with the major focus being on new generation inhibitors. Special emphasis is placed on diketo acids with aromatic and heteroaromatic moieties, diketo acids with nucleobase scaffolds, bis-diketo acids, functionalised naphthyridines and other isosteres of diketo acids. Data pertaining to integrase inhibition and in vitro anti-HIV activity are discussed. Mention is made of drugs in clinical trials, both past (S-1360, L-870,810 and L-870,812 and present (GS-9137 and MK-0518). Other promising drugs, including those from the authors' laboratory, are referred. Resistant mutants arising from key integrase inhibitors and cross-resistance are indicated. **Editors' note: Clinical trials are currently underway of 2 new classes of antiretroviral drugs that target the viral co-receptor CCR5 and the viral integrase enzyme. For the latter, preventing the integration of HIV into human DNA (integration allows HIV to take over the cell machinery) is a critical challenge — and doing so without important side effects is key. If they work, integrase inhibitors could be particularly beneficial for people who have developed HIV resistance to drugs that target HIV's two other major enzymes: reverse transcriptase and protease**

Madan RP, Mesquita PM, Cheshenko N, Jing B, Shende V, Guzman E, Heald T, Keller MJ, Regen SL, Shattock RJ, Herold BC. Molecular Umbrellas: A Novel Class of Candidate Topical Microbicides to Prevent HIV and HSV Infection. *J Virol* 2007 Jul; 81(4):7636-46

Molecular umbrella compounds may function as novel topical microbicides to prevent HIV and HSV (herpes simplex virus) infection. In a preliminary structure-activity investigation, one umbrella compound, designated Spm8CHAS, was identified which inhibited both HIV and HSV infection with no cellular toxicity. The objectives of the current studies were to define its spectrum of antiviral activity, characterize its mechanism of action, and explore the possibility of combining Spm8CHAS with HIV-specific reverse transcriptase inhibitors. Spm8CHAS inhibited infection by laboratory and clinical R5 and X4 clade B and clade C HIV strains in cell culture. Ectocervical tissue explants exposed to HIV-1BaL in the presence of Spm8CHAS were completely protected (IC50=13.6 microg/ml), and transfer of virus to target T-cells via migratory cells was abolished (IC50=3.8 microg/ml). Spm8CHAS inhibited HSV-2 infection of epithelial cells 10,000-fold if present throughout the infection. Notably, adding Spm8CHAS to cultures following HSV entry significantly reduced viral infection, indicating that the drug also acts post-entry. Subsequent studies indicate that Spm8CHAS blocks cell to cell spread of HSV. Confocal microscopy using a fluorescently labelled analogue of Spm8CHAS demonstrated that this conjugate crosses the plasma cell membrane and is transported to the nucleus. Combinations of Spm8CHAS with UC-781 or PMPA in vitro exhibited additive anti-HIV activity with preserved anti-HSV activity. The ability of Spm8CHAS to inhibit primary isolates of HIV, block HSV infection post-entry, and cross cell membranes supports the development of a combination microbicide containing Spm8CHAS with an HIV-specific reverse transcriptase inhibitor to prevent both HIV and HSV by multiple mechanisms. **Editors' note: Molecular umbrella compounds can inhibit both HIV and HSV. In vitro testing of this one - Spm8CHAS - suggests that its ability to inhibit HIV infection (cross-clade), block HIV transfer to T-cells via migratory cells and block HSV spread from cell to cell, if combined with an HIV specific reverse transcriptase inhibitor, would create a potent combo that holds promise for the prevention not only of HIV acquisition but of HSV as well.**

That was *HIV This Week*, signing off.

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