an international migrant as a person living outside their birth country for >= 12 months. The global patterns of human migration have changed substantially in the last half century: 1) increased # countries sending and receiving migrants, 2) accelerated rates of migration, 3) bi-directional migration and migration transitions, 4) diversification of migrant types, and 5) changes in gender patterns of migrants. Along with these profound changes in demography, volume, speed, and purpose of migration come unique challenges in detection, diagnosis, response and management of infectious diseases. Even in the 21st Century infectious diseases account for ~25% of the global mortality burden as well as substantial morbidity. Increasingly these diseases are blind to geopolitical borders. Cyclical pandemics like influenza traverse the globe more rapidly than ever; newly emerged pathogens like SARS represent a constant challenge to public health preparedness and response. Even old diseases like tuberculosis emerge in more lethal drugresistant forms e.g. XDR-TB. These challenges demand new paradigms to global disease control in governance, surveillance and response. The 2005 International Health Regulations and a range of newly formed international networks and partnerships are a testament to the challenges posed by the new era of migration. Our success in combating these microbial threats will depend on our collective effort to organize and respond on ''supra_national'' level.

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Will the next generation end AIDS? (Invited Presentation)

17.001

Role of innate immunity in the control of HIV infection

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While the immunological correlates that contribute to slower HIV disease progression are still unknown, epidemiologic data strongly suggest that particular major histocompatibility complex (MHC) class 1 alleles (including -B27, -B57, and others that fall within the HLA-Bw4 family of HLA-class I B alleles) are highly enriched in subjects who maintain undetectable viral loads in the absence of antiretroviral therapy, Elite controllers. While these MHC molecules interact with T-cell receptors found on cytotoxic CD8+ T cells, they also interact with innate immune receptors, such as the Killer Immunoglobulin like receptors (KIR) found on the surface of innate cytotoxic Natural Killer (NK) cells. Furthermore, the protective effect of MHC class I alleles is amplified in subjects that co-express particular KIRs, with which they are able to interact, resulting in slower progression to AIDS in these individuals compared to those that only possess the KIR or MHC allele alone. Thus it is plausible that NK cells may play a central role in the control of HIV infection. NK cells expand rapidly following acute infection, and specific populations of KIR+ NK cells expand preferentially in subjects that co-express protective KIR/MHC class 1 combinations. This specific KIR3DS1+ NK cell clonal expansion in vitro, these NK cells exhibit a more polyfunctional cytokine profile, and kill MHC class 1 target cells more more aggressively than NK cells from individuals that do not have the protective KIR/HLA combined genotype. However, despite this early epansion of NK cells in the periphery, these cells do not gain access to secondary lymphoid organs, thus providing a safe haven within which the virus is able to replicate unabated by the innate immune system, potentially allowing the virus to establish a chronic infection. These data strongly suggest durable control of HIV infection is associated with an early aggressive deployment of highly licensed antiviral NK cells in the periphery that may provide specific and non-specific control of HIV viral replication in acute infection, while producing large quantities of cytokines and chemokines required for the induction of high quality adaptive immune responses that may then maintain control of HIV replication most likely in contained tissue sites.

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17.002

The Role of T Cell Immunity in the Control of HIV Infection

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The window between transmission and peak viremia, prior to the establishment of viral reservoirs, is the narrow but critical period in which a HIV-1 vaccine must control viral replication, prevent extensive CD4 T cell destruction and curb generalised immune activation. We recently published the results of T cell studies in 4 patients, showing that the first HIV-1 specific T cells detectable just prior to peak viremia can select for complete virus escape in as little as 14 days.

Mathematical modeling of these very rapid rates of T cell escape showed that the contribution of CD8+ T cell mediated killing of productively infected cells was earlier and significantly greater than previously described; calculating that T cells in acute HIV-1 kill as much as 35% of virus-infected cells per day. These first T cell responses often waned rapidly following virus escape leaving, or being succeeded by, T cell responses to epitopes that escaped slowly or were invariant. Here, we present data from an additional 10 patients that extend these observations and demonstrate that early rapid escape from primary HIV-1-specific T cell responses occurs in the majority of patients studied, suggesting that T cells are major contributors to the control of viremia in

acute HIV-1 infection. Additional data will be presented on functional avidity, phenotyping and kinetics across the group over the first 6 months of infection. Discussion will focus on how these results, together with the studies investigating new immunogens may direct more effective design of HIV-1 T cell vaccines. Supported by the NIAD Center for HIV/AIDS Vaccine Immunology grant # U19 AI067854.

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17.003

Understanding Anti-HIV Antibody Targets

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HIV-1 subtype C viruses elicit potent but highly type-specific neutralizing antibodies within the first year of infection. In order to determine the specificity and evolution of these autologous neutralizing antibodies, we examined neutralization escape in four individuals infected with HIV-1 subtype C from the CAPRISA 002 cohort in Durban, South Africa. Early neutralizing responses recognized a very limited number of epitopes, with antibodies that recognize new epitopes evolving sequentially. In addition, only two regions of the envelope were targeted by these antibodies, suggesting there might be common vulnerabilities in the HIV-1 subtype C transmitted envelope. We have shown that type-specific responses have a short term affect on viral load which is lost with the emergence of viral escape mutants. Factors that contribute to the development of broadly cross-reactive neutralizing antibodies, those which would ideally be elicited by an HIV vaccine, are largely unknown. We have examined the evolution of neutralization breadth in the CAPRISA 002 cohort, and shown that cross-neutralizing antibodies develop in about a quarter of infected individuals by 3 years post-infection. Generally breadth develops incrementally suggesting the possibility that multiple antibodies mediate breadth, and/or that breadth is conferred by the maturation of a single specificity. In one case, the development of breadth could be attributed to a single neutralizing antibody specificity. In the CAPRISA 002 cohort, as well as in a cross-sectional cohort of chronically infected individuals, we have explored the targets of cross-reactive antibodies which mediate breadth using an array of methodologies including peptide and protein adsorptions and the use of chimeric viruses. We have shown that multiple epitopes on the envelope glycoprotein are involved in the cross-reactive neutralization elicited during natural HIV-1 infection, many of which are yet to be determined.

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17.004

The Hope and Progress in Microbicides and Pre-Exposure Prophylaxis to Prevent HIV

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Even with a growing recognition that HIV doesn't discriminate by race, gender, socioeconomic status or sex orientation, the developing world accounts for 90% of the global HIV burden. Sub-Saharan Africa, which accounts for two-thirds of the global HIV infections, Injecting Drug Users, Men who have Sex with Men, and Commercial Sex Workers bare a disproportionate burden of the HIV epidemic. Recent HIV surveillance studies in African countries at best show stabilization of the epidemic or at worst, slight increases in countries like Uganda.

Clearly, the HIV research community recognizes that additional new biomedical prevention modalities are required to augment existing HIV prevention strategies.

Incidence modeling based on as relatively low efficacy as 30% for a Pre-Exposure Prophylaxis (PrEP) regimen or a topical Microbicide has provides a glimmer of hope based on number of new HIV infections prevented through such new modalities. However, scientists need to prove efficacy for these new regimens first.

Several international collaborations with the developing world have been formed to enable us conduct clinical research that meets international standards. Phase IIB and phase III HIV PrEP and Microbicide trials are being conducted in nine countries globally, involving over 20,000 participants in the various high risk groups and across different HIV transmission routes. Each study is being overseen by regulatory agencies both within the developing and the developed world.

The major lessons learned to date are that; North-South collaborative partnerships are critical to realizing the hope of finding new prevention modalities to be added to the HIV prevention tool kit for the most-at-risk groups. Secondly, with these collaborations, the developing world has developed capacity to conduct of clinical research that conforms to international standards for licensure of new products or change of indication of existing drugs/products in the developing world.

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The H1N1 influenza pandemic (Invited Presentation)

18.001

Historical perspective: Lessons Learned from past Pandemics

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It has been exactly 500 years since the first recognized influenza pandemic appeared and spread around the world in 1510. Since that time, at least 13 additional influenza