Editorial: Highlights of a Year in AIDS

March 01, 2007 | HIV AIDS [1], Infection [2], Vaccines [3]

Dr Laurence is professor of medicine and director of the Laboratory for AIDS Virus Research, New York Presbyterian Hospital–Weill Medical College of Cornell University, New York; senior scientific consultant for programs, amfAR, The Foundation for AIDS Research; and editor in chief of The AIDS Reader.

Here are my choices for key achievements and discoveries in HIV/AIDS, from those which heralded the new year 2006 through the most recent findings in early 2007. Several are updates of reports first mentioned in my editorials over the past year.

**MALE CIRCUMCISION**

Three randomized controlled interventions conducted in Africa among general populations of uncircumcised men found that circumcision afforded a protection rate against acquisition of HIV via penile-vaginal intercourse ranging from 48% to 60% during a mean follow-up of about 18 months.¹⁻³ A retrospective study of Ugandan couples showed that circumcised men were also 30% less likely to transmit HIV to their female partners.³

The results for prevention of female-to-male transmission of HIV are equivalent to protection rates provided by some widely used microbial vaccines. These results argue for directed education and swift implementation. Although concerns have been raised about engendering feelings of invulnerability to HIV infection following this procedure, during the first year following circumcision, men did not engage in more risky sexual behaviors than their uncircumcised counterparts, at least in a Kenyan cohort.⁴

**MULTIDRUG-RESISTANT TUBERCULOSIS**

Resistance to at least isoniazid and rifampin occurs in a median of 1.0% (range, 0% to 14.2%) of the 8.7 million worldwide annual cases of tuberculosis (TB).⁵ It is a huge issue: a person with untreated TB infects, on average, 10 to 15 people each year,⁶ and treatment of resistant disease requires large expenditures for second-line drugs and up to 2 years of therapy. Concern has escalated with identification of extensively (or extremely) drug-resistant TB (XDR-TB) among 102 people in KwaZulu-Natal, South Africa.⁷ All were coinfected with HIV. The first 53 XDR-TB isolates represented 10% of all positive cultures from one rural district, and 52 of the 53 patients died as a result of what was essentially untreatable disease.⁸ These observations illustrate the need for improved worldwide surveillance for drug-resistant TB. This is particularly important among the HIV-infected in countries with high rates of TB drug resistance, such as China, Russia, and India.

**PREEXPOSURE PROPHYLAXIS**

The theme of the XVI International AIDS Conference was "Time to Deliver." In a plenary presentation there, Gita Ramjee⁹ of South Africa suggested extending the ABCs of HIV prevention—A, abstain; B, be faithful; and C, use condoms—to the real world, where compliance with and acceptability of such programs present formidable challenges. She recommended delivery of C, circumcision; D, diaphragm; E, exposure prophylaxis; F, female-controlled methods, such as microbicides; G, genital tract-factor treatments; and H, herpes simplex virus type 2 prevention and treatment, while awaiting development of vaccines for I, immunity.

This is great, although many of the biomedical prevention methods she lists are not yet ready for dissemination. For example, tenofovir was evaluated as preexposure prophylaxis (PrEP) in 936 HIV-negative women from 3 African countries.¹⁰ Two HIV infections were identified in the tenofovir group, versus 6 among placebo recipients. But this was not statistically significant, given a power analysis that failed to anticipate the low incidence of HIV infections in the control group, a salutary occurrence that may, nevertheless, make similar studies prohibitively expensive.

Lack of evidence for efficacy has not stopped many from relying on tenofovir PrEP, however. In 2005, the CDC reported that 7% of uninfected men who have sex with men had taken an AIDS medication before engaging in risky behavior.¹¹ "Taking a T" (tenofovir) appears to be a growing practice in gay dance clubs.¹¹ The risks for selection and spread of resistant strains are clear.

**NOVEL CLASS OF ANTI-HIV DRUGS**

In this issue of The AIDS Reader, the newest protease inhibitor (PI), darunavir (TMC114), is reviewed.
And over the past year, novel drug classes, such as CCR5 coreceptor antagonists and maturation and integrase inhibitors, as well as novel agents in existing classes, such as the NNRTI TMC125 (etravirine), entered into advanced stages of clinical study. How the genetic barriers to selection of drug resistance, synergy with other antiretrovirals, and other factors will play out in combination therapies is an area of active research. For example, the target in HIV for the fusion inhibitor enfuvirtide, the sole agent in this latest class of FDA-approved antiretrovirals, exhibits high and unanticipated genetic variability, which increases in the presence of resistance mutations to NRTIs, NNRTIs, and PIs. In addition, and just as unexpectedly, enfuvirtide markedly increased tipranavir/ritonavir trough drug concentrations.

One promising new agent is the HIV integrase inhibitor MK-0518. It is a diketo acid with no effect on cytochrome CYP3A4, allowing its use in multiple combinations. In a 10-day monotherapy study in treatment-naive persons with HIV RNA levels of less than 5000 copies/mL, at least 50% of patients had HIV RNA levels suppressed to below 400 copies/mL. In a dose-escalation study in antiretroviral therapy–naive patients of MK-0518 versus efavirenz, each combined with tenofovir and lamivudine, all groups showed a greater than 2.2 log \(_{10}\) decline in HIV RNA level and similar increases in CD4+ T-cell counts, although the rate of HIV RNA level reduction was greater with MK-0518.

SIMPLIFICATION STRATEGIES IN HIV TREATMENT

The benefits of and concerns over simplification strategies for both initial treatment of HIV infection and maintenance of chronically infected persons was a prominent topic. A once-daily regimen of tenofovir, emtricitabine, and efavirenz was compared with twice-daily Combivir (zidovudine/lamivudine) plus once-daily efavirenz in a randomized, open-label multicenter study of antiretroviral therapy–naive patients. Achievement and maintenance of HIV RNA levels of less than 400 copies/mL and increases in absolute CD4 counts from baseline over 48 weeks were equivalent. In mid-2006, the FDA approved the first 1-pill-a-day antiretroviral "cocktail," Atripla, which contains emtricitabine (200 mg), tenofovir (300 mg), and efavirenz (600 mg).

Apart from a hoped for improvement in medication adherence, as a PI-sparing regimen lacking stavudine, Atripla may also be less likely to cause lipatrophy, although the neuropsychological side effects linked to efavirenz could be a deterrent. The "forgiveness factor," or period during which drug levels remain above the inhibitory-dose 50% level, should be good, offering the possibility of making up a dose on the day following a missed pill.

Ritonavir-boosted PI monotherapy as maintenance has also been studied. In the majority of participants, virus suppressed by standard combination antiretroviral therapy remains inhibited by lopinavir/ritonavir or atazanavir/ritonavir alone. However, HIV RNA levels "below the bar"—in the 50 to 400 copies/mL range—are more common with monotherapy maintenance than with continued standard antiretroviral therapy. The clinical relevance of these findings remains to be determined.

SAVING LIVES

Antiretroviral therapy saves lives: 2.8 million years of life since 1989 in the United States alone, in fact, based on national surveillance and efficacy data and a state transition probability model. The average survival from an AIDS diagnosis is now in excess of 14 years. The estimated median survival (from age 25) after diagnosis of HIV infection is now in excess of 35 years. Even among persons with late-stage HIV disease and suboptimal responses to antiretroviral therapy—CD4+ cell counts of less than 200/µL and HIV RNA levels of greater than 100,000 copies/mL—maintaining antiretroviral therapy reduces the incidence of AIDS-related events. However, 25% of infected persons in the United States are unaware of their serostatus and of those who are aware, only 57% are receiving care. On this basis, it has been estimated that an additional 740,000 years of life might have been saved in the United States had all patients received appropriate treatment.

In addition, the proportion of deaths attributable to non-AIDS diseases has increased and is related to hepatic and pulmonary conditions and non-AIDS malignancies, with the CD4 count at death increasing over time. Hepatitis C virus (HCV) plays a significant role. A recent study from Philadelphia found that HCV-HIV coinfection is associated with worsening liver disease and higher mortality than HCV or HIV monoinfection. Non–AIDS-related causes now account for one fourth of all deaths of persons with AIDS; this argues for a shift in the health care model for the HIV-infected population.

CD4 COUNT–GUIDED ANTIRETROVIRAL THERAPY

"The assumption that people are just going to be on therapy for the rest of their lives is not a practical assumption," said Clair Rappoport, a member of the Strategies for Management of Antiretroviral Therapy (SMART) protocol committee, one of several CD4-guided strategic treatment interruption (STI) trials released in 2006.
The SMART participants included 5472 predominantly antiretroviral therapy–experienced persons from 318 sites in 33 countries who were randomly assigned to an episodic treatment or a drug conservation (DC) regimen versus a viral suppressive (VS) strategy of continuous therapy (CT). In the DC arm, highly active antiretroviral therapy was stopped when CD4+ cell counts were greater than 350/µL, then restarted if CD4+ cell counts fell below 250/µL. There was a relative risk of 1.9 for death and 2.5 for clinical progression or death in the DC group, or 3.7 events per 100 person-years (PY) in DC versus 1.5 events per 100 PY in VS (P < .0001) when the study was prematurely terminated as a result of increased adverse events in the DC group.

A major criticism was the study design, with selection of a relatively low CD4 count at which to restart therapy. Potential benefits of using a much higher restart number were suggested by the STACCATO (Scheduled TreAtment interruptions Compared to Continuous Therapy Outcome) trial, a randomized trial conducted predominantly in Thailand. Four hundred thirty patients received CT or STI, with the latter maintained as long as the CD4+ cell counts were greater than 350/µL. The median duration of randomized treatment was 21.9 months; drug savings via STI were 61.2%, with significant differences in side effects between the 2 arms. Virologic failure was equivalent: it occurred in 9 of 284 STI and 6 of 146 CT patients. CD4 count-guided therapy clearly deserves further investigation.

HIV AND THE GUT
It began with several presentations at the 12th Conference on Retroviruses and Opportunistic Infections, held in February 2005, attempting to define a unified hypothesis to explain the rapidity and depth of T-cell depletion characteristic of HIV/AIDS. The gut took center stage in speculations concerning HIV immune pathology and remained there throughout 2006. Early studies of the GI tract in simian immunodeficiency virus (SIV)-infected rhesus macaques found a profound but selective depletion of CD4+ T cells in the intestine within days of infection, before any changes in peripheral lymphoid tissues. This was attributed to the fact that SIV, like HIV, replicates optimally in activated CCR5+ memory CD4+ T cells, a cell type abundant in the GI tract. There was a loss of 50% of memory CD4+ T cells from all lymphoid compartments by days 10 to 14 and an 80% loss at day 17. A similar phenomenon appears to occur in the human GI tract following acute HIV infection.

Based on cancer chemotherapy models, CD4+ T-cell reconstitution is limited after such massive depletion. In AIDS, chronic immune activation imposes an additional homeostatic strain, further draining the memory CD4+ T-cell pool. These changes have been tracked by Daniel Douek's group as the group divides HIV immune pathogenesis into 2 stages. There is massive, very rapid loss of memory CD4+ T cells in the acute phase, a result of direct infection of T cells, followed by immune activation and activation-induced cell death in the chronic phase. Circulating lipopolysaccharide has been found in chronically HIV-infected persons, an indicator of microbial translocation from a mucosally compromised gut. In nonpathogenic SIV infection of sooty mangabeys, such translocation was not seen.

Given all this damage, can we ever hope to achieve immune reconstitution in AIDS? If highly active antiretroviral therapy partially restores mucosal immunity, this could suppress microbe trafficking as one source of chronic immune activation. In fact, lipopolysaccharide levels do decline after antiretroviral therapy, although they still remain above the levels seen in uninfected persons. But despite suppressive treatment with highly active antiretroviral therapy during acute and early infection for 1 to 7 years, 50% to 60% depletion of lamina propria lymphocytes persists. This has led to the ominous prediction that “although clinically silent over the short term, the long-term consequences of the persistence of this lesion may emerge as the HIV-1-infected population survives longer as a result of the benefits of HAART.” More research is needed into the efficacy of antiretroviral therapy in the GI tract, as well as T-cell homing to gut tissue, and the influence of microbial products in maintaining an activated immune state there. For example, interleukin 15 can stimulate production of effector memory cells with gut-homing potential in monkeys.

References:


Source URL: http://www.patientcareonline.com/articles/editorial-highlights-year-aids

Links: