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Contents

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Nontuberculous mycobacteria: an overview

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Mycobacterial species other than *M. tuberculosis* and *M. leprae* are called nontuberculous mycobacteria (NTM). They are free-living organisms that are ubiquitous in the environment. They can affect both immunocompetent and immunocompromised persons. It is believed that these organisms are acquired from the environment and there are no solid data demonstrating human to human or animal to human transmission.

Patients with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are especially vulnerable. NTM can also cause outbreaks of infection in hospitals affecting renal patients on dialysis, wound infection in operations such as cardiac surgery, liposuction and injection or intravenous device related infections. All these arise from contamination of reusable devices or solutions with NTM from environment.

Isolation of NTM from clinical specimens may represent colonisation, infection or pseudo-infection due to contamination of specimens during collection or in the laboratory.

Classification

In 1950s, Timpe and Runyon proposed the first classification system for these organisms. They divided human isolates of NTM into groups on the basis of growth rates, colony morphology, and pigmentation in the presence and absence of light. For example, if an organism took less than 7 days to grow, it is classified as rapid growing mycobacteria.

Nowadays, the NTM are commonly classified based on their propensity to involve various organs:

- Lungs: *M. avium complex* (MAC) and *M. kansasii*
- Lymph nodes: MAC, *M. scrofulaceum*, *M. malmoense*
- Skin: *M. marinum*, *M. ulcerans* and rapid growers
- Disseminated disease: MAC, *M. kansasii*, *M. chelonae*, *M. haemophilum*

Epidemiology

NTM is not a notifiable disease in Hong Kong, therefore the frequency of disease due to different species of NTM is unknown.

A nationwide survey by Centers for Disease Control and Prevention (CDC) of US in the 1980s found that the most commonly recognised species were MAC (61 percent), rapid growers (19 percent), *M. kansasii* (10 percent) and other NTM (10 percent).

In children with lymphadenitis, MAC and *M. scrofulaceum* accounted for 97% of the cases.

MAC accounted for more than 90% of the disseminated NTM infection in HIV patients

Clinical features and diagnosis

Pulmonary disease

Three clinical presentations have been described:

1. In older male with pre-existing lung disease.

The disease resembles typical tuberculosis clinically and radiographically, with cough, weight loss, upper lobe infiltrates, and cavities. Symptoms are generally less severe than tuberculosis. Lung destruction may be quite extensive at the time of diagnosis due to the relatively indolent nature of MAC lung disease. The most common species isolated are MAC and *M. kansasii*.

2. In elderly women with bronchiectasis.

Productive cough is the most common symptom. Radiographic findings include multiple scattered nodular opacities with bronchiectasis and are more severe in the middle and lingular lobes. MAC is the most common pathogen.

3. Predominantly in non-smoking women over age 50 who have interstitial patterns on chest radiography involving upper lobes.

Chronic cough may be the only symptom. The disease may progress slowly into respiratory failure. *M. abscessus* and *M. fortuitum* can be the culprit.

Diagnosis

Diagnosis of pulmonary NTM infection can be difficult due to underlying lung disease and the propensity of these organisms to colonise without causing infection. The official statement of the American Thoracic Society had proposed the following diagnostic criteria for symptomatic patients with radiographic abnormalities.

A. If three sputum/bronchial wash results are available from the previous 12 months:

1. Three positive cultures with negative acid-fast bacilli (AFB) smear results or
2. Two positive cultures and one positive AFB smear

B. If only one bronchial wash is available:

1. Positive culture with a 2+, 3+, or 4+ AFB smear or 2+, 3+, or 4+ growth on solid media

C. If sputum/bronchial wash evaluations are nondiagnostic or another disease cannot be excluded:

1. Transbronchial or lung biopsy yielding nontuberculous mycobacteria (NTM) or
2. Biopsy showing mycobacterial histopathologic features (granulomatous inflammation and/or AFB) and one or more sputums or bronchial washings are positive for an NTM, even in low numbers

Extra-pulmonary disease

Lymphadenitis

NTM involving cervical nodes of children 1-5 years is the commonest form of lymphadenitis in immunocompetent subjects. The child is usually afebrile with the involved lymph nodes enlarged for weeks to months. The diagnosis can be made by AFB culture and the best way is to perform excisional biopsy which is the best treatment as well.

Skin and soft tissue infection

Cutaneous infection caused by NTM is most common after localised trauma or surgery. The NTM species that most commonly cause localised infections of the skin and subcutaneous tissue are rapid growers. Diagnosis is made by culture of the specific pathogen from drainage material or tissue biopsy.

Postoperative infection caused by *M. fortuitum* has been reported in sternotomy for cardiac surgery, augmentation mammoplasty, hip replacement, cervical laminectomy and pacemaker insertion etc.

M. marinum is the cause of “swimming pool granuloma” or “fish tank granuloma”. The lesions usually appear as papules on an extremity, especially on the elbows, knees, and dorsum of feet and hands, progressing to ulceration and scar formation. The organisms may be introduced into the skin by scratches or puncture wounds from salt water fish, shrimp, fins, etc. Diagnosis is made from biopsy material, histological examination, and culture.

senior in position has a negative impact, with medical students scoring higher than attending physicians or professors. In addition, it was found that failure of senior physicians to practice good hand hygiene negatively affected adherence among junior colleagues as well.

Points to note: The advantages of hand cleansing are clear. Unfortunately, despite the ready availability of sinks and portable cleansing solutions, many physicians continue to have poor compliance to hand hygiene practices. Adherence to good hand hygiene often is lowest where risk is highest. Active campaigns involving observation, embarrassment, and even penalties might prove useful in future.

Song JH, Jung SI, Ko KS, et al. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). Antimicrob Agents Chemother. 2004; 48: 2101-7.

Antibiotic-resistant Streptococcus pneumoniae is a major health problem in many countries. Particularly in Asia, resistance rates against both penicillin and macrolides are increasing in an alarming rate. In this study, researchers from the 14 centers collaborating in the Asian Network for Surveillance of Resistant Pathogens focused on resistant strains of pneumococci collected between January 2000 and June 2001. Using the broth microdilution test according to current NCCLS guidelines, they determined the drug susceptibility to 14 antibiotics of 685 isolates from patients with community-acquired pneumococcal infections.

Overall, 52.4% of the isolates were non-susceptible to penicillin (23.0% intermediate, 29.4% highly resistant), compared with 35.9% (18.1% intermediate, 17.8% highly resistant) in 1996-1997. The highest resistance rates were seen in Vietnam, South Korea, Hong Kong, and Taiwan; the lowest, in India and the Philippines. On multivariate analysis, age ≤5 years, underlying chronic pulmonary condition, malignancy, and treatment with steroids were independent risk factors for infections caused by resistant pneumococci. In addition, 54.9% of isolates overall were not susceptible to erythromycin (1.8% intermediate, 53.1% highly resistant). Relatively low non-susceptibility rates were found for ceftriaxone (2.8%), amoxicillin-clavulanate (7.0%), and the fluoroquinolones (<2% for levofloxacin, moxifloxacin, and gatifloxacin; 6.0% for ciprofloxacin). Multidrug resistance, defined as non-susceptibility to at least three classes of antibiotics, was detected in 26.8% of isolates, predominantly those from Vietnam, Hong Kong, Taiwan, and Korea.

Points to note: This survey reveals the increasing rates of antimicrobial-resistant pneumococci in Asia. Unfortunately, as the data of the study originated few years ago, the problem could be even larger by now. Of special concern is the prevalence of resistance against quinolones seen in the study.

Bukreyev A, Lamirande EW, Buchholz UJ, et al. Mucosal immunisation of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. Lancet. 2004; 363: 2122-7.

ter Meulen J, Bakker AB, van den Brink EN, et al. Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. Lancet. 2004; 363: 2139-41.

The emergence and global spread of the SARS coronavirus (SARS-CoV) have prompted much research on preventive strategies. Recently, mucosal immunisation and immunoprophylaxis have generated promising results in animal models.

Bukreyev and colleagues modified a live attenuated vaccine virus, BHPIV3, to express the envelope spike (S) protein of SARS-CoV and also constructed a control vaccine (BHPIV3/Ctrl). BHPIV3 is derived from a bovine parainfluenza virus and bears protective antigens identical to those in human parainfluenza virus type 3 (HPIV3). The researchers administered BHPIV3/Ctrl or BHPIV3/SARS-S vaccine intranasally and intratracheally to eight adult African green monkeys with no preexisting antibodies against HPIV3 or SARS-CoV. The animals were then challenged with live SARS-CoV 28 days later. All animals that received BHPIV3/SARS-S developed SARS-CoV-neutralising serum antibodies. In addition, animals that received control vaccine shed SARS-CoV from the respiratory tract for 5 to 7 days after challenge; no monkeys that received BHPIV3/SARS-S shed virus on any day.

Ter Meulen and colleagues generated a human IgG1 monoclonal antibody (CR3014) that could neutralise SARS-Co-V in vitro. Ferrets challenged with live SARS-CoV that was preincubated with CR3014 developed no lung lesions and did not shed SARS-CoV in their throats, unlike animals challenged with SARS-CoV and control antibody mixture. Ferrets given single intraperitoneal injections of CR3014 at 24 hours before intratracheal challenge with live virus had significantly less virus in lung homogenates than did control animals; no throat shedding occurred in the majority of animals given CR3014.

Points to note: SARS-CoV remains a threat to humans because the virus persists in animal reservoirs. In this primate study, a single mucosal immunisation of the respiratory tract induced local and systemic immunity and protected against shedding after a challenge. BHPIV3/SARS-S might be effective in infants and children but is unlikely to be immunogenic in adults, because antibodies to the vaccine vector (parainfluenza) would inhibit its replication. Passive immunisation with monoclonal antibodies might be useful in persons who have been exposed to SARS-CoV. The results of further animal or human studies are eagerly awaited.

Complications
Gynecomastia in male patients with HIV is largely related to hypogonadism (Biglia et al). No association with antiretroviral therapy was found. The overall rate of gynecomastia was found to be similar to that previously described for the general population.
HIV infection was identified as an independent risk factor for preeclampsia and fetal death in utero (Suy et al). It is found to be associated with chronic maternal use of antiretrovirals, occurring predominantly in woman who had been on antiretroviral therapy before they became pregnant, and not associated with the use of antiretroviral therapy in woman identified during pregnancy.
Osteonecrosis or aseptic necrosis of large bones such as the hip has been described in patients with HIV. In a large epidemiologic study conducted by Mary-Krause et al., a significant relationship between the duration of exposure to antiretroviral therapy and the development of osteonecrosis was found. Osteonecrosis was also more likely to occur in patients with low CD4 count nadirs.

Coinfection with viral hepatitis
A number of studies presented in 2004 have shown that pegylated interferon plus ribavirin is effective in the treatment of hepatitis C in HIV-coinfected patients. The APRICOT study showed that the major predictors of response were related to hepatitis C (Rodriguez-Torres et al). Patients infected with hepatitis C genotypes 2 or 3 were much likely to respond to pegylated interferon plus ribavirin than those infected with genotype 1 (odds ratio 3.37, P <0.001). Furthermore, the hepatitis C viral load was also predictive. Patients who had hepatitis C RNA levels <800,000 copies/ml were 3.56 times more likely to respond to pegylated interferon than patients who had higher hepatitis C RNA levels. In this study, HIV-related factors including HIV viral load and CD4 count were not predictive of response to hepatitis C treatment, although the design of the study was such that relatively few patients with very low CD4 count were included. Further study is needed to determine whether higher CD4 count is associated with a better response to pegylated interferon plus ribavirin therapy for hepatitis C.
For lamivudine-resistant hepatitis B coinfection, a 4-year pilot study of adefovir therapy showed that the proportion of patients who achieved suppression of hepatitis B replication increased steadily throughout follow-up (Benhamou et al). At week 192 of the study, 59% patients achieved a hepatitis B DNA <1000 copies/ml and 70% patients achieved a normalisation of alanine aminotransferase. There was no evidence of emergence of resistance to adefovir in hepatitis B or more importantly, the emergence of HIV-associated K65R resistance mutation. In addition, the proportion of patients who had improvement in liver histology increased over time (33% at week 48; 50% at week 192). This data suggests that continued use of adefovir in coinfected patients with active hepatitis B infection is beneficial, and that the benefit is sustained.

ID journal scan September 2004

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Fawzi WW, Msamanga GI, Spiegelman D, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. N Engl J Med. 2004; 351: 23-32.
Nutritional deficiencies in HIV-infected individuals have been associated with adverse clinical outcomes. In 1995, Fawzi and colleagues began a double-blind, randomised, placebo-controlled trial to evaluate the effect of vitamin supplementation on disease progression in a group of HIV-infected pregnant women in Tanzania.

The researchers enrolled 1078 women with a mean CD4 count of 400 cells/mm^3. Participants were randomised to receive daily vitamin A (and carotene), multivitamins (vitamins B, C, and E), both vitamin A and multivitamins, or placebo. The multivitamins regimen was the only intervention that showed significant benefit. Progression to WHO stage 4 disease or death was 24.7% in the multivitamins arm compared with 31.1% in the placebo arm. The beneficial effect of multivitamins was apparent within the first 12 to 24 months and persisted for up to 4 years. Vitamin A alone was not associated with benefit; in fact women receiving both vitamin A and multivitamins had slightly worse outcomes than those receiving multivitamins alone.

Points to note: In this African setting, multivitamins (excluding vitamin A) were associated with a slower progression to AIDS. Vitamin supplementation is a useful component in a comprehensive care plan, but clearly is no replacement for antiretroviral therapy. The surprisingly poor performance of vitamin A challenges the common belief that all vitamin supplements are beneficial.

Pittet D, Simon A, Hugonnet S, et al. Hand hygiene among physicians: performance, beliefs, and perceptions. Ann Intern Med. 2004; 141: 1-8.
Despite the undisputed importance of proper hand hygiene in preventing nosocomial infections, physicians remain markedly non-compliant to hand-hygiene policies. Researchers recently used direct observation followed by questionnaires to study factors affecting hand-cleansing behavior among a group of physicians at a Geneva teaching hospital.
Opportunities for hand hygiene practices (hand cleansing, changing of gloves) included treatment of different patients, prior to handling of intravascular devices, and examination of clean body sites following examination of contaminated sites. Overall guideline adherence was 57%. Independent variables predicting better adherence were awareness of being watched, a positive attitude about hand cleansing, perception of being a role model, and carrying hand-rub solution in a pocket. Adherence varied greatly among specialties, being best in internal medicine, pediatrics, and geriatrics and worst in surgery, anesthesiology, and emergency medicine. As far as practicing hand hygiene is concerned, being

M. ulcerans causes indolent necrotic lesions of the skin and underlying tissue. The lesions occur most commonly in children and young adults and often result in severe deformities of the extremities.

Disseminated disease
Disseminated disease usually occurs in immunocompromised patients. MAC, *M. kansasii*, rapid growers, etc. have been reported in this setting with MAC the commonest. Fever, weight loss and bone pain are common presentations.
Disseminated infection caused by rapid growers usually presented with fever and skin lesions.
The diagnosis can be confirmed by culturing the organism from blood, bone marrow or a skin lesion.

Treatment
MAC
The use of in vitro susceptibility result to guide treatment is still controversial because correlation between pretreatment susceptibility test result and response has only been demonstrated for newer macrolides and rifabutin. Tentative breakpoint for interpretation of susceptibility have been suggested for newer macrolides and rifabutin, however newer macrolides are highly concentrated within infected macrophages such that serum concentration of these antibiotics are unlikely to predict their activity in vivo.
A number of antimicrobial agents have activity against MAC, including: newer macrolides, rifabutin, ethambutol, ciprofloxacin, and aminoglycosides. Initial therapy usually consists of clarithromycin / azithromycin + ethambutol + rifampicin / rifabutin.
The duration of treatment for disseminated MAC in HIV-infected patients without immune reconstitution is life-long. Once immune reconstitution happened as a result of HAART, treatment can be stopped provided there has been at least 12 months of therapy and six months of immune reconstitution has passed.
For pulmonary MAC disease, the regimen recommended for disseminated MAC is also applicable. The duration of the treatment for pulmonary MAC should be 12 months after culture turns negative.

M. kansasii
Routine susceptibility testing of *M. kansasii* should include only rifampin, because currently used resistance breakpoints for isoniazid and streptomycin often give misleading results and methods for the other drugs have not been established.

Pulmonary disease
M. kansasii is the second most common NTM causing pulmonary disease. The American Thoracic Society recommendation for the treatment of this infection is a three-drug combination consisting of isoniazid (300 mg QD) + rifampin (600 mg QD) + ethambutol (25 mg/kg per day for two months, then 15 mg/kg per day). Therapy is given for 18 months, with a minimum of 12 months of culture negativity.

Extrapulmonary disease
Affected lymph nodes should be excised. If disease recurred then further excision followed by chemotherapy for 9 to 24 months is required. Infection at sites other than superficial lymph nodes should be treated by chemotherapy for at least 9 months.

Rapid growers
Treatment of rapid growers should be based on in vitro susceptibility result. Rapid growers are not susceptible to the first-line anti-tuberculous drugs. Drugs used for susceptibility test should include amikacin, cefoxitin, imipenem, a sulphonamide, newer macrolides, fluoroquinolone, and doxycycline.

Skin and soft tissue disease
For localised disease, surgical debridement should be followed by intravenous treatment for 2-4 weeks and followed by oral medicines for total of 3-6 months. For disseminated disease, daily aminoglycosides or imipenem plus clarithromycin should be administered for first 2-4 weeks, then clarithromycin for total of 6 months.

Pulmonary disease
They are rare and there is paucity of evidence to give definite guidance. Cure may not be attainable without surgery.

References
1. Timpe A, Runyon EH. The relationship of atypical acid-fast bacteria to human disease: A preliminary report. J Lab Clin Med 1954:44202-9
2. Wallace RJ Jr., O'Brien R, Glasnoth J, et al. American Thoracic Society: Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 1997;156:S1-25
3. Schlossberg D. (Editor). Tuberculosis and nontuberculous mycobacterial infections. Fourth Edition. 1999 WB Saunders

What we should know about ESBLs

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With the widespread use of extended-spectrum cephalosporins (ESCs), bacterial strains which produce extended spectrum beta-lactamases (ESBLs) have been increasing worldwide. ESBLs hydrolyze all cephalosporins, penicillins and aztreonam except cephamycin. These enzymes are most commonly found in Klebsiella pneumoniae and Escherichia coli, but they have now been detected in other species of Enterobacteriaceae like Proteus mirabilis, and in non-Enterobacteriaceae such as Pseudomonas aeruginosa.

Infections with ESBL-producing organisms are usually hospital-acquired, especially in ICU. These also occur in nursing homes, geriatric and paediatric wards, and oncology units. The common infections include all the infections caused by gram-negative organisms such as urinary tract infections, peritonitis, cholangitis, intra-abdominal abscess, pneumonia, catheter-associated blood stream infections. Several reports described various risk factors responsible which included longer duration of hospitalisation, ICU care, ventilator care, presence of a central venous catheter or urinary catheter, and previous use of antimicrobials especially of ESCs.

Clinically relevant ESBL-mediated resistance is not always detectable in routine susceptibility tests, as the MICs of oxyimino-cephalosporins for ESBL-producers are often low (0.5-2.0 mcg/ml). Several detection methods for ESBL have been proposed, however, there is no reporting guideline for bacteria other than E. coli and Klebsiella spp. The NCCLS has issued recommendations for the screening and confirmation of ESBL in isolates of E. coli and Klebsiella spp. by using disk diffusion and broth dilution methods. However, the following problems exist:

Which agent should be used for screening?

[1] Cefpodoxime is the most sensitive of the screening agent, many of the screen-positive isolates are ESBL nonproducers. The NCCLS (2002) changed the breakpoints for cefpodoxime (≤ 22mm to ≤ 17mm, ≥ 2mcg/ml to ≥ 8mcg/ml) to reduce the number of false-positive results.

[2] Presence of ESBLs can be masked by the expression of chromosomal AmpC beta-lactamases, which are produced by e.g. Enterobacter, Serratia, Citrobacter spp. Plasmid-mediated AmpC β-lactamases are also found in E. coli and K. pneumoniae recently. Cefepime is stable to the enzyme but labile to ESBLs, hence theoretically a more reliable detection agent to reduce the number of false-negative results. E-test combining cefepime and clavulanate have recently been marketed for testing specific TEM-24 Enterobacter, though its wider application awaits to be confirmed.

Whether a screening result should be reported or not?

Targeted antibiotics could be administered unnecessarily if the clinical laboratory reports a positive ESBL screening result and the isolate subsequently proves to be ESBL negative. On the other hand, appropriate therapy may have been delayed for 24 hours if a positive screening result is withheld and the isolate is subsequently confirmed as ESBL positive. Most local laboratories will not report the screening result, the 'delay' may not be too significant as the laboratory will proceed to the sensitivity test against the second line agents while performing the confirmatory ESBL test.

The emergence and spread of ESBL-producing strains have led to questions regarding the optimal therapy for infections caused by these strains and especially the empirical treatment of suspected gram-negative infections. Although many reports have described the treatment results of the infections caused by ESBL-producing organisms, there has been no randomised prospective study to date. The ESBL producers often reveal susceptibility to some ESCs but show inoculunm effect in vitro, and the MICs rose even within the susceptible range. Clinical failures of treatment have been repeatedly reported. Potential therapeutic options for the treatment of infections with ESBL-producing organisms include β-lactam-β-lactamase inhibitor combinations, cephamycin, carbapenem, fluoroquinolones and aminoglycosides.

Carbapenem has been the most successful drug in many of the published reports and is the drug of choice in serious infections caused by ESBL-producing organisms. The use of fluroquinolones is limited by the rising incidence of quinolone resistance among the ESBL-producers. Aminoglycosides can be used as combination therapy for the serious infections. Resistance against ESCs is often associated with resistance to aminoglycosides as well. Cephamycin is resistant against hydrolysis by ESBLs and does not show the inoculum effect in vitro. However, clinical experience is lacking for this attractive option. Lastly, the β-lactam-β-lactamase inhibitor combination is subject to inoculum effect in vitro, and several clinical reports have described clinical failures with mortality rates exceeding 50%. Thus this combination has a limitation for the treatment of severe infections so far.

References

1. Bradford PA et al. Extended–spectrum β-lactamases in the 21st century: characterisation, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev. 2001;14:933-51.
2. Lautenbach E, Patel JB, Bilker WB, et al. Extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae: Risk factors for infection and impact of resistance on outcomes. Clin Infect Dis. 2001;32:1162-71.
3. Menashe G et al. Clinical significance and impact on mortality of ESBL-producing Enterobacteriaceae isolates in nosocomial bacteraemia. Scand J Infect Dis 2001; 33(3): 188-93.

Report from the XV International AIDS Conference, Bangkok, July 2004

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Global epidemiology

UNAIDS and the World Health Organisation published the updated estimates of global epidemiology of HIV/AIDS infection. The estimated number of people living with HIV and AIDS continued to increase through 2003, and now approaches 40 million. In addition, the prevalence of HIV among adults aged 15 to 49 is now just over 1% in the world. Well over 50% of infected individuals live in sub-Saharan Africa, with Asia the next most affected region. Almost one quarter of new infections occurred in Asia, implying that there was a rapid growth in that region. In 2003, about 4.8 million new infections and 2.9 million deaths occurred. In Asia, the main drivers of HIV epidemic are injection-drug users, men who have sex with men and heterosexual transmission from sex workers to their clients and then from the clients to their partners.

Antiretroviral regimens

The Gilead 903 Study compared tenofovir with stavudine, each given with lamivudine and efavirenz in 600 treatment-naïve individuals in a randomised double-blinded manner (Gallant et al). After 144 weeks, 73% on tenofovir arm and 69% on stavudine arm had HIV viral load <50 copies/ml in the intent-to-treat analysis. The toxicity of tenofovir and stavudine are somewhat different. There was a small but significant increase in total limb fat in the tenofovir arm, whereas a decrease in total limb fat was noticed in the stavudine arm. This data suggests that tenofovir is less likely to be associated with lipoatrophy. Tenofovir also has little or no effect on triglyceride level.

Data from the Dupont 006 study showed that efavirenz/zidovudine/lamivudine was consistently superior to indinavir/zidovudine/lamivudine during 168 weeks of follow-up (Tashima et al). At 168 weeks, around 54% patients on the efavirenz based regimen could maintain a viral load <400 copies/ml.

Treatment interruptions

The HIV-NAT 001.4 trial investigated several ways of guiding treatment interruption (Ananworanich et al). All recruited patients had a CD4 count >350 cells/mm^3 and a viral load <50 copies/ml for at least 6 months. They were randomised either to continuous HAART using NRTI plus boosted saquinavir, or to CD4- guided therapy in which they stopped therapy and only reinitiated their regimen if their CD4 count declined below 350 cells/mm^3, or to a 1-week-on/1-week-off treatment interruption scheme. None of the patients on continuous therapy and 4% of the patients on CD4 guided therapy had virological failure at week 72. There were no differences between continuous therapy and CD4 guided therapy interruption in terms of adverse events or quality of life.

Another novel form of treatment interruption was presented. Castagna et al examined 50 patients who had CD4 count >500 cells/mm3 and who had measurable viral load on a lamivudine-containing regimen, with documented lamivudine resistance, and who requested treatment interruption. Patients were randomised to either stop all antiretroviral therapy or stop all therapy except lamivudine monotherapy at 300mg/day. The study demonstrated a slower CD4 count decline in patients with lamivudine monotherapy compared with those with all therapy stopped. In addition, the viral load increase was also lower in patients who were maintained on lamivudine monotherapy. Lamivudine monotherapy might select M184V mutation, which has been associated with reduced viral fitness, and that could lead to a slower decline in the CD4 count over time compared with complete treatment interruption.

Resistance issues in prevention of mother-to child transmission (MTCT)

Focus has been made on the issue of emerging problem of drug resistance in women who had received short-course therapy to prevent MTCT of HIV infection. The Treatment Options Preservation Study examined whether a "cocktail" of antiretroviral agents administered following single-dose nevirapine might prevent the emergence of nevirapine resistance (McIntyre et al). All subjects received single-dose nevirapine, once to the mothers and once to the baby. In one arm, mothers received no other drugs; in the second arm, the mothers and the infants received 4 days of zidovudine/lamivudine; and in the third arm, the mothers and the babies received 7 days of zidovudine/lamivudine. This study showed that the arms given 4-7 days of zidovudine/lamivudine (two arms combined together) and single-dose nevirapine had a lower incidence of nevirapine resistance compared with the arm on single-dose nevirapine alone (9.3% vs 50%, P=0.001). This study has important implications in terms of policy for use of single-dose nevirapine in the resource-poor countries.

New antiretroviral drugs

A number of entry inhibitors are in the stages of clinical development. Data on the Pfizer CCR5 inhibitors, UK-427, 857, showed a relationship between the area under the plasma concentration-time curve and the extent of antiviral activity (Fatkenheuer et al).

Oral administration of tenofovir was demonstrated to protect infant macaques against SIV infection by oral exposure (Van Rompay et al). A pilot study of tenofovir vaginal gel demonstrated that it was safe and well tolerated in both HIV-infected and HIV-uninfected women (Mayer et al), supporting further study of its effectiveness as a woman-controlled HIV prevention method. Other studies are now under way to evaluate the effectiveness of oral tenofovir as pre-exposure prophylaxis against sexual transmission in individuals at high risk, such as sex workers or men who have sex with men.