

HIV/AIDS

Antiretroviral Newsletter



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The aim of this biannual newsletter is to provide health workers in the Region with a brief, up-to-date summary of the latest developments in antiretroviral therapies.

New agents

Abacavir (Ziagen) - nucleoside reverse transcriptase inhibitor

The recommended dose of abacavir is 300 mg twice daily.

In key research studies, abacavir therapy has been evaluated in chronically HIV-infected patients as part of triple therapy with two other nucleosides (AZT and 3TC or Combivir[®]) and as part of dual therapy with a protease inhibitor (indinavir, saquinavir SGC, ritonavir, nelfinavir or amprenavir). In a study of the new protease inhibitor amprenavir with abacavir, 41 treatment-naïve people took amprenavir (1 200 mg twice daily) and abacavir for 6 months. In an intention-to-treat analysis, 80% had HIV-RNA below 500 copies/ml and 68% were below 50 copies/ml. The mean increase in CD4+ lymphocytes was 100 cells/mm³.

562 patients were enrolled into a randomized, double-blind study comparing abacavir/Combivir[®] with indinavir/Combivir[®] (CNA3005). Intent-to-treat analysis at week 24 showed 65% of both groups had viral loads below 400 copies/ml.

The incidence of hypersensitivity reaction in people taking abacavir is 3%. It is characterized by rash, fever, malaise, fatigue and gastrointestinal symptoms such as nausea, vomiting, and diarrhoea. It generally occurs within four weeks of starting abacavir, and usually resolves within one to two days after ceasing abacavir treatment. Abacavir should be stopped immediately and NOT resumed since rechallenge can produce a life-threatening anaphylactic reaction.

Cost per year in the USA: US\$ 3 500.

Amprenavir - protease inhibitor

The recommended dose of amprenavir is 1 200 mg (eight 150 mg caps) twice daily with or without food. It is available as 50 mg and 150 mg soft gel capsules, and as 150 mg/ml oral solution.

In one of the two licensing studies, 221 treatment naïve participants were randomized to AZT/3TC/amprenavir or AZT/3TC/placebo. Median baseline viral loads were 4.61 log and 4.74 log and CD4+ lymphocyte counts were 435 and 409 for the amprenavir and placebo groups, respectively. Intention-to-treat analysis at 16 weeks found that, in the amprenavir group, 60% of those on amprenavir treatment were below 50 copies/ml compared with 9% in the placebo group

Amprenavir (1 200 mg bid), abacavir (300 mg bid) and efavirenz (600 mg once daily) were given as salvage therapy to 99 people who had at least 20 weeks prior PI therapy and detectable plasma RNA following at least 12 weeks on their current PI containing regimen. Median baseline HIV-RNA was 5.06 log (100 000 copies) and median CD4 was 169. Participants with baseline viral load <40 000 copies/ml and those who were NNRTI-naïve at baseline responded better to the salvage regimen. At week 16, 53% of those with the lower baseline viral load had HIV-RNA <400 copies, compared with 23% in the group with initial viral load > 40 000 copies/ml.

Combination protease inhibitor therapy was studied in 33 individuals who received amprenavir with one of three protease inhibitors or as a single protease inhibitor with AZT/3TC added after three weeks. All participants had baseline HIV-RNA of >10 000 copies/ml. The protease inhibitors used were saquinavir soft gel caps, indinavir and nelfinavir taken at standard doses and amprenavir, taken as 800 mg TID. At 24 weeks, reductions in viral load were 2.72 log in the saquinavir

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arm, 2.25 log in the indinavir arm and 1.81 log in the nelfinavir arm. Ten out of 22 people remained below 50 copies/ml at week 24.

The safety profile of amprenavir in 606 subjects who had been exposed to amprenavir for at least 12 weeks, and 41 for at least 48 weeks was recently reviewed. The most frequently reported adverse events were nausea (51%), diarrhoea (37%), rash (28%), oral paraesthesia (25%), headache (24%), fatigue (23%) and vomiting (23%). The majority of adverse events were mild to moderate (grade 1 or 2), early onset (2-21 days after commencing therapy) and transient in nature (3-46 days duration). Laboratory abnormalities reported most frequently from the two phase III trials were increased transaminase levels (overall incidence \leq 5%), and hypertriglyceridemia (3%).

The I50V mutation was observed in vitro to be a key amprenavir resistance mutation. In addition to this, the 154V, 154L, I84V, I50V, M46I and I47V mutations are associated with phenotypic resistance to amprenavir. Some of these are also associated with resistance to other PIs.

Cost per year in the USA: US\$ 6 000.

Efavirenz

Efavirenz is the newest of the non-nucleoside reverse transcriptase inhibitors (NNRTI) and will be marketed under the tradename Sustiva in Europe and North America and as Stocrin in the rest of the world.

The recommended dose of efavirenz is 600 mg, taken as three 200 mg capsules once a day before bed, with or without food. Taking the drug with food may increase drug levels in some people by up to 50%.

Efavirenz is contra-indicated in pregnancy. Studies of animals treated with efavirenz showed high rates of birth defects. A pivotal study (DMP 266-006) enrolled 450 participants in an open-label, randomised comparison of efavirenz and AZT/3TC *versus* indinavir and AZT/3TC *versus* efavirenz and indinavir, all in standard doses. The participants were protease inhibitor, NNRTI and 3TC naive. At baseline, the mean CD4 count was 345 cells and mean viral load was 58 884 copies/ml. After 48 weeks, 71% of people on efavirenz/AZT/3TC had viral loads below 400 copies compared to 48% on indinavir/AZT/3TC and 54% on EFV/IDV by intent-to-treat analysis. For viral load below 50 copies, the figures are 65%, 43% and 48% respectively. Increase in CD4 count was approximately 175 cells in all three arms. There were more study medication related discontinuations in the indinavir/AZT/3TC arm (38%) compared to approximately 21% in the other arms.

CNS-related symptoms, mostly grade 1 in severity, were reported in 55% of efavirenz recipients. These were confusion, dizziness, agitation, amnesia, depersonalisation, euphoria, hallucinations, insomnia, somnolence, impaired concentration, abnormal dreaming and stupor. Approximately 30% of EFV recipients experienced rash resulting in four discontinuations.

Efavirenz was studied in 57 children, with an average age of 8 years, who took efavirenz/nelfinavir plus two NRTIs. Doses were adjusted based on drug levels at weeks two and six. Intent-to-treat analysis at week 20 found two-thirds of the children were below 400 copies/ml and median CD4 count rise was 106 cells.

K103N is the predominant resistance mutation observed in vivo among efavirenz treatment failures. In studies DMP 226-003 and DMP 266-004, treatment failure virus isolates carrying K103N, V108I and/or Y188L mutations showed a >20 fold increase in the in vitro IC50 for efavirenz compared to pre-therapy isolates. These isolates were also resistant to nevirapine and delavirdine.

Cost per year in the USA: US\$ 4 700.

Treatment strategies

A three-year follow up study of 33 patients taking indinavir (800 mg TID) with AZT (200 mg TID) and 3TC (150 mg BID) was recently carried out. Participants in this study were AZT pre-treated, and protease inhibitor and 3TC naive. There were 11 withdrawals, 7 due to viral rebound. 39% had at least one episode of nephrolithiasis during the 36 months and 19% had lipodystrophy as assessed by the study investigators.

Results

% undetectable (Intent-to-treat analysis)			
Week	Week 100	Week 124	Week 148
<500 copies/ml	78% (25/32)	68% (21/31)	67% (20/30)
<50 copies/ml	66% (21/32)	55% (17/31)	67% (20/30)

Saquinavir SGC (Fortovase) taken twice daily is being compared to three times per day in the TID-BID study, with results at 32 weeks being reported.

840 treatment naive and experienced participants were randomized to one of three study arms.

ARM A: Fortovase 1 200 mg TID + 2 new nucleosides
 ARM B: Fortovase 1 600 mg BID + 2 new nucleosides
 ARM C: Fortovase 1 200 mg BID + nelfinavir 1 250 mg BID + 1 new nucleoside.

At 32 weeks, in 494 participants, there was no virological difference in outcome in the three treatment arms.

The 48-week data on the combination of efavirenz, AZT and 3TC showed superiority of this regimen over an indinavir (IDV)-based triple therapy regimen. Study 043 is an open-label multicenter trial in which d4T is substituted for AZT. Standard doses of efavirenz, d4T and 3TC were given to antiretroviral-naive subjects with an entry HIV-RNA level greater than 4 logs. The Study will follow 68 patients for 2 years. Data have been reported on the first 42 patients enrolled for 24 weeks. The proportion of patients with HIV-RNA <400 copies/ml at week 24 was 100% in the observed data (OD) analysis and 92% in the intent-to-treat (ITT) analysis. Using an ultrasensitive assay with a limit of

detection of 50 copies/ml, the proportions below detection were 97% and 89% in the OD and the ITT analyses, respectively. These data are comparable to those presented for the combination of efavirenz, AZT and 3TC.

In another PI versus non-PI comparison, The Atlantic Study randomized 300 participants with baseline CD4+ count > 200 CD4 cells/mm and plasma HIV RNA > 500 copies/ml to d4T/ddI/3TC, d4T/ddI/nevirapine (NVP), or d4T/ddI/indinavir for 72 weeks. Preliminary 24-week data presented demonstrate equivalence of the three regimens.

An induction/maintenance strategy is being studied in an ongoing trial of AZT/3TC/abacavir following initial therapy with a PI-based combination. The study randomized people who maintain viral load less than 50 copies/ml for 6 months to continue their PI regimen or switch to AZT/3TC/abacavir. Preliminary data at 4-6 months of follow-up shows virologic failures in the two groups are equivalent.

Cost per year in the USA: US \$ 6 800.

Average cost of ARV drugs (in USA)

ANTIRETROVIRAL	COST/MONTH (US\$)	COST/YEAR (US\$)
Zidovudine	280	3,360
Didanosine	202	2,424
Zalcitabine	210	2,520
Stavudine	259	3,108
3TC	239	2,868
Combivir (AZT+3TC)	519	6,228
Abacavir	295	3,540
Delavirdine	223	2,676
Nevirapine	255	3,060
Efavirenz	389	4,668
Saquinavir (Invirase)	570	6,840
Saquinavir (Fortovase)	565	6,780
Indinavir	435	5,220
Ritonavir	612	7,344
Nelfinavir	563	6,756

Source: The 1999 HIV Drug Guide, Jan/Feb 1999.

Journal reviews

Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1

Murphy RL, Sommadossi J-P, Lamson M, et al. *J Infect Dis* 179(5):1116-1123, May 1999.

In a prospective study, 24 HIV-infected patients on stable nucleoside therapy or no therapy were given indinavir (800 mg q8h) for 7 days. Nevirapine was then added (200 mg/day for 7 days, then 200 mg BID).

Pharmacokinetic parameters were assessed at day 7 and day 36. The addition of nevirapine resulted in an 11% reduction in median indinavir plasma C_{max}, a 47.5% reduction in median indinavir plasma C_{min}, and a 27.7% decrease in median indinavir plasma AUC. Indinavir did not affect nevirapine plasma clearance or steady-state trough concentrations. Ten of twelve patients treated with indinavir/nevirapine alone for at least 24 weeks had HIV RNA reductions to <20 copies/ml. The authors conclude that indinavir dose modifications may not be required when it is co-administered with nevirapine.

Outcome and predictors of failure of highly active antiretroviral therapy: one-year follow-up of a cohort of human immunodeficiency virus type 1-infected persons

Wit FWNM, van Leeuwen R, Weverling GJ, et al. *J Infect Dis* 179(4):790-798, April 1999.

In a retrospective analysis, 271 protease inhibitor (PI)-naive patients taking antiretroviral regimens with at least one PI were studied. 78% had prior nucleoside exposure. After 48 weeks, in an intent-to-treat analysis, 75% had HIV RNA <1000 copies/ml, based on the PI initially given to the patient, the proportion <1000 copies/ml was 84% for indinavir, 89% for zidovudine, 59% for saquinavir (taken as Invirase), and 89% for zidovudine/saquinavir.

The proportion of patients with virological treatment failure (defined as those whose HIV RNA never declined below 1000 copies/ml, or rebounded above 1000 copies/ml) was 40% overall; 27% for indinavir, 30% for zidovudine, 59% for saquinavir, and 32% for zidovudine/saquinavir. In a multivariate analysis, factors associated with virological failure were baseline HIV RNA level, baseline CD4+ count and use of saquinavir as the only PI.

It was reported that 53% of patients modified their regimen during the first 48 weeks. Of these, 42% were because of toxicities, and 24% because of an increase in HIV RNA. Saquinavir regimens were changed most often due to rising viral load and zidovudine-containing regimens were most often changed because of intolerance. The overall proportion who changed therapy was 44% for those who originally received indinavir, 64% for zidovudine, 62% for saquinavir, and 30% for zidovudine/saquinavir.

HIV-1 rebound during interruption of highly active antiretroviral therapy has no deleterious effect on reinitiated therapy

Neumann AU, Tubiana R, Calvez V, et al. *AIDS* 13(6):677-83, April 1999.

In the Comet Study, 10 antiretroviral-naive patients initiated therapy with zidovudine, lamivudine, and indinavir for 28 days, followed by interruption of all drugs for 28 days and then reintroduction of the same regimen. The rate of viral decline was measured during each period of therapy, and was found not to differ significantly. The mean T_{1/2} of viral decay during the rapid initial phase was 1.48 days during the first

treatment period and 1.62 days during the second period. During the slower second phase of viral decay, the mean $T_{1/2}$ was 8.93 days during the first treatment period and 7.97 days during the second period. No new resistance mutations developed during the study. The authors conclude that a 1-month interruption of all drugs in a HAART regimen does not adversely affect the virologic efficacy of the same regimen once reinitiated.

Abnormal body-fat distribution in HIV-1-infected children on antiretrovirals

Babi FE, Regan AM, Pelton SI *Lancet* 353(9160):1243-1244, April 1999.

The authors conducted a questionnaire survey of 1 644 children receiving combination therapy that included a PI and 1069 children on a non-PI-containing regimen. Twenty-eight cases of body fat redistribution were reported from a total of 16 investigator sites. 24 of these children were receiving a PI and 4 were not. The duration of PI therapy ranged from 1 to 14 months, with a gradually increasing prevalence over time. Sites of abnormal body fat distribution were the abdomen (17 cases), upper back (12 cases), and face (10 cases).

Drugs in development

T20, a fusion inhibitor, inhibits HIV replication by blocking virus entry into CD4 lymphocytes. Early studies used T20 intravenously but new research suggests that it is also effective when given subcutaneously. A small dose-ranging study demonstrated viral load reduction of 1.5 \log_{10} after one month at the highest dose studied. Resistance to this compound developed reasonably quickly and further studies are planned using it in combination with other antiretrovirals, initially in salvage regimens.

ABT-378, is a second-generation protease inhibitor currently in phase II studies. In vitro studies have shown ABT-378 is ten times more potent than ritonavir. In combination with small doses of ritonavir, drug levels of ABT 378 are sustained such that once daily dosing may be possible. The most common side effect is loose stools or diarrhoea, which occurred in approximately one-third of phase II study participants.

In vitro studies suggest that ABT-378 is cross-resistant with other protease inhibitors. Initial mutations can be at codons 50 and 46, or at codons 84, 46 and 10. Both mutation patterns produce 7-10 fold resistance and are followed by mutations common to other protease inhibitors.

An access scheme is likely during 2000, with licensing predicted for the same year.

AG 1549 is a new non-nucleoside reverse transcriptase inhibitor.

Phase 1 trials suggest that AG 1549 is ten times more potent than current NNRTIs. This drug is active against HIV variants with single mutations at codons K103N or V106A or L100I, which confer resistance to other NNRTIs.

In vitro studies show that BMS 232632 is a highly potent protease inhibitor. Studies in HIV-negative volunteers found good bioavailability of 57% to 80% which may allow for once daily dosing. BMS expects the daily dose to fit into a single tablet.

Tipranavir is a new protease inhibitor. There are phase II studies in planning in the USA and Europe. A pediatric formulation of the drug is also being developed. Tipranavir reduces delavirdine levels by 95% and studies so far suggest a TID dosing schedule.

The resistance pattern of tipranavir is still the subject of study.

New treatment guidelines

6 May 1999: The Panel on Clinical Practices for the Treatment of HIV Infection, convened by the Department of Health and Human Resources in the USA, has just updated its guidelines. The full text is available at www.hivatis.org/guidelines/AA

May 1999: The British HIV Association has published a discussion draft of its 1999 guidelines. The full document is available from the joint BHIVA/National AIDS Manual website at www.aidsmap.com

Key points are:

- therapy is recommended at CD4 count <350 cells/mm³ or viral load >55 000 copies/ml;
- treatment of acute HIV infection is recommended;
- a regimen including a non-nucleoside RTI may have advantages as first line therapy but there is insufficient data as to which NNRTI is best.

Internet web sites

www.natap.org Site of National AIDS Treatment Advocacy Project (NY). Free e-mail and paper-based monthly reports. This site was used in part as a reference source for the preparation of this newsletter

www.aidsmap.com Monthly online treatment updates and fact sheets

www.medscape.com Extensive, well-arranged site. Includes drug interaction "calculator".

www.infoweb.com Links to many HIV sites



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