National AIDS Treatment Advocacy Project

Indinavir + AZT/3TC: Merck's study #035

Abstract Th.B.931 -- **POTENT AND SUSTAINED ANTIRETROVIRAL ACTIVITY OF INDINAVIR AZT AND 3TC**"
Authors--R Gulick, J Mellors, D Havlir, J Eron, C Gonzalez, D McMahon, D Richman, F Valentine, J Rooney, L Jonas, A Meibohm, E Emini, J Chodakewtiz

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The first results presented for this study were by Dr. Roy Gulick, a study investigator at NYU, at the Human Retrovirus Conference in January 1996. The detailed report of the data presented in January is available on the NATAP web-site in the article entitled Daily Highlights--Days 3 & 4, which is listed with other reports under Human Retrovirus Conference, and should add to the perspective of interpreting the data here. Six months of data were presented in January. In Vancouver, and detailed in this article, Dr. Gulick reported 48 weeks of data.

The objectives of this trial are to evaluate safety, efficacy, magnitude of antiretroviral activity, duration of antiretroviral activity and the development of resistance.

Study design
Double-blind, placebo-controlled, randomized--comparing:

- indinavir (IDV) 800 mg every 8 hours + AZT 200 mg every 8 hours + 3TC
- 150 mg bid (every 12 hrs.)
- IDV 800 mg every 8 hrs (monotherapy)
- AZT 200 mg every 8 hours + 3TC 150 mg every 12 hrs
- 3TC naive
- CD4 50-400/mm3
- HIV RNA 20,000 or above copies/ml (Roche PCR kit)
- 6 months or more previous AZT therapy

Baseline characteristics

	totals (n=91)	**IDV+AZT+3TC** (n=32)	**IDV** (n=28)	**AZT+3TC** (n=31)
HIV RNA PCR (median)*				
--copies/ml	41,385	39,320	37,335	43,490
--log10 copies/ml	4.62	4.59	4.57	4.64
CD4/mm3 (median)	144	131	156	144

Prior AZT therapy (median months)	29.7	28.8	29.8	31.2

*based on 90 patients for whom information is available

Discontinuation Rate

7 of 97 discontinued after up to 60 weeks of therapy

- adverse event (nausea) : 1
- Lost to follow-up : 1
- Non-study medications* : 2
- Patient request
- (declining CD4 cell counts) : 3

*Rifampin, cytotoxic chemotherapy

Safety profile

Adverse Event	**totals** (n=97)	**IDV+AZT+3TC** (n=33)	**IDV** (n=33)	**AZT+3TC** (n=31)
Anemia or Neutropenia*	6	1	1	4
Nausea*		2	1	0
Headache*	1	1	0	0
Total Bilirubin (2.5 to 5.1 mg/dl)	22	12	9	1
Clinical Nephrolithiasis**	9	4	4	1

*requiring dose reduction of AZT+3TC or addition of growth factor

**all nine patients continued study drugs, 2 underwent indinavir dose reductions

Merck has reported--

"Nephrolithiasis can cause flank pain, hematuria (blood in urine). Reported to date--approximately 4% (79/2205) of patients receiving indinavir in clinical trials have developed Nephrolithiasis. In general, these events were not associated with renal dysfunction and resolved with adequate hydration and temporary interruption of therapy (e.g. 1-3 days). Following an acute episode (kidney stones can develop), 9.2% (7/76) of patients discontinued therapy.

Asymptomatic hyperbilirubinemia (total bilirubin above 2.4 mg/dl) reported predominantly as elevated indirect bilirubin, has occurred in approximately 10% of patients treated with indinavir in clinical trials. In less than 1% this was associated with elevations in ALT or AST.

Hyperbilirubinemia and nephrolithiasis occurred more frequently at doses exceeding the currently recommended daily dose of 800 mg/3X-day."

Commentary
It has been reported that the elevated bilirubin usually subsides after a brief time on drug. Merck has said they do not believe there are longer-term consequences related to this side effect. Long-term safety data will address this issue as it becomes available. The long-term data for all protease inhibitors will be the truer measure of any long-term side effects or toxicities, as well as for the durability of efficacy. Again, because of the potential for kidney stones, it is highly recommended that adequate hydration be strictly adhered to when taking indinavir. Merck has recommended drinking at least 48 ounces of water per day; it is also recommended that you drink at least 8-10 ounces at the time of taking the indinavir pills.
--end of commentary

THE DATA

HIV RNA and CD4 Changes (median) from Baseline (median for all 3 treatment groups--41,100 copies; median CD4 for all 3 treatment groups-- 142 cells)

IDV+AZT+3TC--

N	RNA		N	CD4
-	8 weeks 2.0 log reduction	- -	8 weeks	75 cell increase
30	24 weeks 2.2 log	- 28	24 weeks	120
26	36 weeks 2.0 log	- 21	36 weeks	120
7	48 weeks*2.3 log	- 7	44 weeks*	215

* Again, the RNA and CD4 changes at weeks 48 and 44 are based on only 7 and 9 patients, respectively.

IDV--

N	RNA		N	CD4
-	8 weeks 1.6 log reduction	-	8 weeks	100 cell increase
27	24 weeks 0.8 log	- 26	24 weeks	100
24	36 weeks 1.0 log	- 19	36 weeks	120
9	48 weeks* 1.6 log	- 9	44 weeks*	160

*Again, the RNA and CD4 changes at weeks 48 and 44, respectively, are based on only 9 patients

AZT+3TC--

N	RNA	N	CD4
-	8 weeks** 0.75 log reduction	- -	8 weeks 40 cell increase
27	24 weeks 0.75	- 27	24 weeks 20
27	36 weeks 0.50	- 18	36 weeks 0
8	48 weeks 0.50	- 9	44 weeks 10

**At 2 weeks, the RNA was reduced by 1.5 log, but quickly rebounded to a 1.0 log reduction at 4 weeks, and of course it rebounded to a 0.75 log reduction at 8 weeks

Commentary
This study suggests, as well as other studies suggest, that for individuals with extensive prior treatment experience (the participants in this study had about 2 yrs & 5 months AZT experience) and relatively low CD4 counts (144 cells in this study) merely adding another nucleoside to a current regimen of 1 nucleoside may not offer significantly lasting benefits. In Vancouver, there was some disagreement and controversy among researchers over when a treatment naive individual should begin therapy and with which therapy. However, for individuals who are treatment-experienced and with moderately or advanced disease progression, the considerations are different regarding when to initiate protease inhibitor therapy and with which other accompanying drug(s).

For a fuller discussion, see the NATAP booklet Perspectives on Viral Load (HIV RNA and When To Initiate Therapy: a discussion of data, how to use viral load tests, how to interpret results"; or, you can read the article on the NATAP web-site Viral Load: Important information", which was written prior to updated revisions incorporated into the booklet.

% of Reductions in HIV RNA below detectability (500 copies/ml is the lowest measure of the test used by Merck in this instance

IDV+AZT+3TC

- 8 weeks 75%
- 24 weeks 90% (n=30)
- 36 weeks 81% (n=26)
- 48 weeks 86% (n=7)*

IDV

- 8 weeks 42%
- 24 weeks 40% (n=27)
- 36 weeks 40% (n=24)
- 48 weeks 57% (n=9)*

AZT+3TC

- 8 weeks 10%
- 24 weeks 0% (n=27)
- 36 weeks 2% (n=27)
- 48 weeks 0% (n=8)

*The same reminder, these figures are based on a very small amount of patients

Future directions for indinavir studies in planning stages:

- vertical transmission: safety, tolerability and pharmacokinetics in
- pregnant and non-pregnant women
- combination therapy of indinavir with the new more potent formulation of saquinavir, which is still in clinical trials
- a continuation of ongoing pediatric studies
- early disease