

NATAPE-Resist 50 RNA Reduces Death Risk 83% in MDR

Cohort Studies Support Sub-50 RNA Goal for Salvage Therapy

"virologic suppression, rather than partial viral load control, should therefore be pursued in every three-class resistant patient" if a suppressive regimen can be fashioned. Reaching a viral load under 50 prolonged survival even in people with double or triple class-wide resistance. Slashed the risk of death 83%....

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Two cohort studies from separate groups in Rome found that reaching a viral load below 50 copies/mL after treatment failure with multidrug-resistant virus greatly raises the chance of longer AIDS-free survival [1,2]. The results support updated guidelines specifying an undetectable viral load as a primary goal of rescue therapy.

Researchers from Rome's Lazzaro Spallanzani Institute studied 1392 people who had a resistance genotype after virologic failure from 1999 through 2004 then started a new regimen [1]. Follow-up lasted through the end of 2006. At genotyping 37.5% of the cohort had AIDS, median CD4 count stood at 304 cells, and median viral load measured 4.3 log. During follow-up 134 people (9.6%) died, 210 (15.1%) died or progressed to AIDS, and 817 (58.7%) reached a viral load below 50 copies.

Among people who attained a sub-50 load, 92% survived through 72 months of follow-up, compared with 63% who did not reach a sub-50 load, a highly significant difference ($P < 0.0001$). Among 403 people with a CD4 count under 200 at genotyping, 87% of those who got under 50 copies survived for 72 months compared with 44% of those who did not get under 50 copies ($P < 0.0001$).

Multivariate analysis determined that pushing the HIV load under 50 lowered the risk of death 54% (95% confidence interval [CI] 0.27 to 0.76, $P = 0.02$) and lowered the risk of AIDS or death 57% (95% CI 0.28 to 0.65, $P < 0.001$). Every 100-cell higher CD4 count at genotyping cut the death risk 31% (95% 0.58 to 0.81, $P < 0.0001$). Every additional 10 years of age raised the death risk 41% ($P = 0.012$), and an AIDS diagnosis before genotyping raised the risk 79% ($P = 0.017$).

In the group that got their viral load under 50 copies, getting there faster trimmed the death risk 3.6% for every faster month (95% CI -6.8% to -0.2%, $P = 0.036$). Every fewer month to sub-50 suppression lowered the risk of AIDS or death 4.4% monthly (95% CI -7.4% to -1.2%, $P = 0.016$).

These investigators defined class-wide nucleoside resistance as having 3 or more nucleoside-related mutations, class-wide nonnucleoside resistance as having 1 or more nonnucleoside mutations, and class-wide protease inhibitor (PI) resistance as having 3 or more major PI mutations. By those criteria 443 people (31.8%) had class-wide nucleoside resistance, 407 (29.2%) had class-wide nonnucleoside resistance, and 155 (11.1%) had class-wide PI resistance.

Among people with no class-wide resistance or class-wide resistance to one antiretroviral class, 87% survived through 72 months of follow-up, compared with 78% of those with class-wide resistance to two or three classes ($P = 0.003$). But reaching a viral load under 50 prolonged survival even in people with double or triple class-wide resistance. In that group getting under 50 copies slashed the risk of death 83% ($P < 0.0001$) and the risk of AIDS or death 80% ($P < 0.0001$).

Because faster viral suppression during salvage significantly favored longer survival, the researchers urged clinicians to construct the most potent salvage regimen possible after multiple treatment failure. They endorsed an undetectable

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viral load as a treatment goal for people with multiclass-resistant virus.

Clinicians at Rome's Catholic University also found that attaining a viral load below 50 copies after emergence of triple-class resistance independently favored AIDS-free survival in two statistical analyses [2]. This 150-person study included people having their first genotype after virologic failure, but all had at least one major mutation to nucleosides, nonnucleosides, and PIs. The group had a median of two thymidine analog mutations, one nonnucleoside mutation, and two PI mutations. While 44% had more than three thymidine analog mutations, 36% had more than three major PI mutations. They had taken a median of five antiretrovirals (range three to 11), had a median viral load of 3.92 log (about 8300 copies) at genotyping, and a median CD4 count of 300.

During cumulative follow-up of 515 person-years, 106 people (71%) reached a sub-50 viral load. Sixteen people had a new AIDS diagnosis in that time. The Catholic University investigators used two multivariate analyses to pinpoint independent predictors of AIDS-free survival, one adjusted for viral load at genotyping and one adjusted for an AIDS diagnosis before genotyping.

The first analysis determined that notching a sub-50 load lowered the risk of AIDS or death 86% (HR 0.14, 95% CI 0.03 to 0.75, $P = 0.02$), while the second analysis figured a 68% lower chance of AIDS or death with a sub-50 load (HR 0.32, 95% CI 0.10 to 0.99, $P = 0.049$). The second analysis also determined that an AIDS diagnosis before genotyping boosted the risk of AIDS or death 10.23 times (95% CI 2.68 to 39.09, $P < 0.001$). Factors that did not affect AIDS-free survival were lowest-ever CD4 count, CD4 count at genotyping, gender, age, viral load at failure, and calendar year. As in the other study [1], faster time to a sub-50 load significantly favored AIDS-free survival ($P = 0.013$).

The researchers argued that "virologic suppression, rather than partial viral load control, should therefore be pursued in every three-class resistant patient" if a suppressive regimen can be fashioned.

References

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