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EXPERT REVIEWS

Mortality rates in HIV-infected patients with second failure of antiretroviral therapy are still high: a lesson from NA-ACCORD

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Evaluation of: Deeks SG, Gange SJ, Kitahata MM *et al.* Trends in multidrug treatment failure and subsequent mortality among antiretroviral therapy-experienced patients with HIV infection in North America. *Clin. Infect. Dis.* 49, 1582–1590 (2009).

In clinical practice, a significant proportion of HIV-infected patients still experience treatment failure during antiretroviral therapy (ART). There is limited information regarding the second treatment failure and its mortality rate. This article assessed the findings of a recently published paper describing analyzed data from the North American AIDS Cohort Collaboration on Research and Design. A total of 7159 out of 36,188 patients who received ART had a second virologic failure from ART. Although the risk of second failure decreased from 1996 to 2005 owing to the evolution of ART, the cumulative mortality at 5 years after onset of second failure was 26%. Strategies to prevent treatment failure are urgently needed in order to minimize the mortality among HIV-infected patients receiving ART.

Keywords: antiretroviral therapy • HIV • mortality • treatment failure • virologic failure

Summary of methods & results

This article reviews the study by Deeks *et al.* [1], summarizes the paper's key findings and discusses the implications for clinical practice. The study analyzed data from a large cohort and described the incidence and predictors of progression to, and the rates and predictors of mortality after the onset of a second virologic failure. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a regional collaboration of single- and multisite cohorts that includes over 90,000 patients from more than 50 sites throughout the USA and Canada, and was designed to enhance the quality, cost–effectiveness and speed of HIV/AIDS observational cohort studies [2]. Patients with a second episode of virologic failure were identified from this cohort, and multivariate Cox regression analysis was used to assess factors associated with time to second failure and the time to death after the onset of virologic failure of a second regimen. Virologic failure was defined as a HIV RNA level greater than 1000 copies/ml.

Out of 36,188 HIV-infected patients who were administered combination antiretroviral therapy (ART), 17,820 experienced an initial episode of virologic failure and 13,165 had a regimen change after the first virologic failure. Most of the patients had a first regimen failure with a protease inhibitor-based regimen. The majority of patients had exposure to mono- or dual nucleoside reverse-transcriptase analogues before receipt of the first standard combination regimen. This issue led to the paralleled analysis of patients who were antiretroviral-naive before the first combination regimen for all critical outcomes analysis. Out of 13,165 patients who switched to a second regimen, 7159 subsequently experienced a second virologic failure. At the time of second virologic failure, the median (interquartile range) CD4 cell count was 244 (120–405) cells/mm^3 and most patients (66%)

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had been exposed to all three classes of antiretroviral agents. The risk of having a second virologic failure decreased dramatically over time. The crude incidence of second treatment failure during 1996–1997 was 56 events per 100 person-years and was 16 events per 100 person-years in 2005. In a Cox regression analysis, these temporal trends remained strong and statistically significant. Similar trends were observed in the subset of 5087 patients who were treatment-naive before receipt of their first regimen and who eventually modified therapy after an initial episode of virologic failure. Factors associated with a lower risk of second treatment failure were a longer time between the initiation and modification of therapy and a higher CD4 cell count. A higher viral load at the time that the regimen was switched was associated with an increased risk of second treatment failure. Gender, age, AIDS, initial regimen type and a higher viral load at the first virologic failure time point were not associated with second treatment failure in multivariate analysis.

Of the 7159 subjects who experienced a second failure, there were 1532 deaths observed during 25,722 person-years of follow-up after second treatment failure. The cumulative mortality was 5% at 1 year and 26% at 5 years. The crude incidence of mortality among those who experienced a second failure during 1996–1997 was 6.5 deaths per 100 person-years and decreased to five deaths per 100 person-years in 2003. In a multivariate analysis, there was a statistically significant trend towards a lower risk of death among those with second failure in later years. A similar trend was observed in the analysis of 2050 patients who had no treatment experience before the initiation of combination therapy. Predictors of mortality after second virologic failure included a lower CD4 cell count, a higher viral load and AIDS, all at the time of second virologic failure. These predictors of mortality remained of similar magnitude and significance when the analysis was restricted to those who were antiretroviral treatment naive before receipt of their first regimen. Gender, pretherapy CD4 cell count, pretherapy viral load and regimen type were not associated with mortality in multivariate analysis.

Expert commentary

This study has demonstrated the incidence and outcomes of second treatment failure among patients receiving ART across North America. Cohort study of HIV-infected patients can provide key estimates of the disease progression, long-term treatment outcomes and mortality [3]. The results have been analyzed from a large sample size cohort that included a diverse population of patients in real-life clinical practices. Thus, the results may be a more feasible reflection of the treatment outcomes in clinical practice since the data from clinical trials may not be representative of patients in clinical practice [4,5]. The large sample size of this study allows the authors to assess supposedly rare events, such as mortality, or perform an analysis in some specific subpopulations.

The incidence of second virologic failure decreased dramatically over time. However, the risk of mortality after a second failure was still high, and higher than the mortality among the larger NA-ACCORD population of all treatment-naive patients starting therapy [6]. Although the mortality after first virologic failure was not described in this study, the high mortality after second virologic failure was a concern. The mortality rates among those patients who experienced second failure gradually decreased over time whereas the rate of second failure markedly decreased over time, mainly due to the evolution of ART in recent years [7,8]. Plasma HIV RNA levels, CD4 cell counts and AIDS remain independent risk factors for mortality after second failure, which are similar to the risk factors for mortality in treatment-naive patients and those with first virologic failure described in previous studies [9–14]. However, as the authors noted, the observation periods ended in 2005, just prior to the introduction of several new antiretroviral agents with proven efficacy in highly treatment-experienced patients. Thus, the results from this study may not be applicable for second treatment failure in the current situation, particularly in settings where new antiretroviral agents, such as darunavir, raltegravir, maraviroc and etravirine, are available. Hence, the mortality after second failure may be lower than that in this study if the patients can use the new agents in the third regimens. By contrast, the results from this study may be more currently applicable for some countries, such as Thailand, Brazil and China, where therapeutic options and therapeutic strategies for the first and second regimens are improved but the new agents are not yet available or accessible [15–17]. In order to decrease mortality among these patients, interventions to prevent treatment failure (either first or second failure) are crucial and even more important than aggressive therapy strategies for patients who encounter second failure. Without the availability and accessibility of new antiretroviral drugs, the latter strategies may be too late.

Five-year view

During the next 5 years, the quality of HIV care, as well as the antiretroviral regimens for both first regimens and second regimens, will continue to improve, in term of efficacy, durability, tolerability, convenience and barrier to drug resistance. For example, there are currently more options for the preferred regimens recommended in the current Department of Health and Human Services guidelines for treatment-naive patients [101]. Given the more-potent and better-tolerated regimens, as well as the earlier initiation of therapy and better monitoring of response to therapy, the incidence of second failure will further decrease significantly in the next 5 years. The mortality after experiencing second failure is expected to be dramatically decreased when new antiretroviral agents become available, the optimal regimen is used, and the patients can adhere to the regimen well. However, once second failure occurs, similar factors including plasma HIV RNA levels, CD4 cell counts and AIDS at the time of failure will continue to be independent risk factors for mortality.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- In clinical practice, a significant proportion of HIV-infected patients experience a second virologic failure after receiving the second antiretroviral regimen.
- The North American AIDS Cohort Collaboration on Research and Design cohort showed that the risk of second failure decreased from 1996 to 2005, mainly owing to the evolution of antiretroviral therapy (ART).
- However, the cumulative mortality at 5 years after onset of second failure was still high at 26%.
- Strategies to prevent treatment failure are urgently needed in order to minimize the mortality among HIV-infected patients receiving ART.
- The results from this study may not be applicable for second treatment failure in the current situation in which new antiretroviral agents, such as darunavir, raltegravir, maraviroc and etravirine, are available.
- Interventions to prevent treatment failure (either first or second failure) are crucial to decrease the mortality rate, particularly in the setting in which new antiretroviral drugs are not yet available and accessible.

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