RESEARCH LETTER

Triple-Class Antiretroviral Agent Resistance in a Large Cohort: Prevalence and Clinical Outcomes

Triple-class resistance constitutes a major treatment challenge in the era of highly active antiretroviral therapy (HAART).[1-3] It is found in antiretroviral naïve individuals due to transmission of drug-resistant strains, although the majority of cases have extensive prior antiretroviral exposure.[4] Despite the increasing use of potent combinations, inadequate suppression of viremia is likely to be associated with risks of acquiring further resistant mutations and an increased risk of disease progression and mortality.[5] In the recently published update of the UK Collaborative HIV (UK CHIC) study, it was shown that extensive virologic failure to the 3 main antiretroviral classes occurred in 9.2% of individuals over 10 years in routine clinical practice.[6] To investigate this further, our objective was to establish the prevalence, risk factors for acquisition, and clinical outcomes of individuals with triple-class resistance.

Methods. Virco resistance tests (Virco BVBA, Mechelen, Belguim) denoting genotypic and phenotypic profiles have been used routinely in our institution since 1997. Clinic policy demands that all patients have baseline resistance tests performed at the time of human immunodeficiency virus (HIV) diagnosis and at any point when a patient who was currently receiving antiretroviral therapy attains a detectable viral load, ie, greater than 50 copies/mL. We defined triple-class resistance as the presence of 3 or more mutations or 1 or more mutation from each of the major antiretroviral classes—nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and/or protease inhibitors—at any time point (it is well known that resistance mutations vary in their impact on response to antiretroviral therapy). For simplicity, we counted all mutations regardless of whether they were major or minor, and as a result we may have overestimated the prevalence of triple-class resistance. Drug resistance mutations were identified using International AIDS Society guidelines, and HAART was defined as more than 3 antiretroviral agents in accordance with standard practice (dual nucleoside analogues alone are not considered HAART). In addition, a comprehensive retrospective note review was performed for each individual with appropriate ethical approval.

Results. We found that since 1997, a total of 7715 resistance tests have been performed, corresponding to 3476 individuals infected with HIV type 1. Of these individuals, 231 (6.6%) had triple-class resistance according to our criteria. A total of 170 individuals (73.6%) had been

Table 1. Cause of Deaths in Individuals With Triple-Class Resistance

Cause of Death	No. of Individuals
Malignancy	6
End-stage human immunodeficiency virus	6
Sepsis	5
Decompensated liver disease	2
Other	4

previously exposed to either mono-agent (single nucleoside) or dual-agent (double nucleoside) antiretroviral therapy in the pre-HAART era, with the majority having commenced antiretroviral therapy between 1994 and 1998. From the 231 patients with triple-class resistance, 16 individuals (7%) had documented difficulties with adherence, 14 (6%) experienced toxic effects, which also affected adherence, and in 1 case (0.4%) treatment was complicated by a severe opportunistic infection. Five individuals (2%) intermittently ceased therapy of their own accord. One individual who was naïve to antiretroviral therapy had a baseline resistance test result indicating primary acquisition of multiresistant virus.

In this cohort, 23 patients (10%) have died (**Table 1**); the mortality incidence is 11.5 (95% confidence interval, 7.3-17.2) per 1000 patient-years using person-years at risk as a denominator, which was defined as first entry into the cohort and censored at either death or last entry into the cohort. Despite the presence of triple-class resistance, it had been possible to construct a regimen (including experimental drugs) in which viral replication was suppressed below the limits of detection in 44% of the patients. In addition, 69% of the remaining individuals have maintained a stable CD4 lymphocyte count above 200 cells/µL despite the presence of triple-class resistance (**Table 2**).

Comment. These data suggest that overall, the incidence of triple-class resistance is low and fairly constant over time, occurring at 17.1 (95% confidence interval, 15.0-19.5) per 1000 patient-years of all individuals undergoing resistance testing (representing a prevalence of 7.2%), although this may be a feature of the differing definitions of triple-class resistance in each of the studies on this subject. Our data are in contrast to other assumptions that multiple drug–resistant HIV is an increasing problem, in danger of outstripping the ability of the pharmaceutical industry to develop novel therapies. The main drivers for triple-class resistance appear to be suboptimal initial therapy in which single or dual nucleoside analogues were used at the outset, in conjunction with hard gel saquinavir in the mid-1990s, and later, further unboosted protease inhibitor therapy. In our study, the number of individuals developing triple-class resistance, having initiated therapy with HAART, is lower than the recent published data on this subject,[5,6] although in all cases it appears to occur slowly.

Table 2. The Latest CD4 Lymphocyte Count and Viral Load for Each Individual With Triple-Class Resistance (Less 23 Patients Who Had Died)

Latest CD4 Lymphocyte Count, Cells/µL	Latest Viral Load, Copies/mL	Individuals, No. (%)
>200	<50	77 (37)
<200	<50	15 (7)
>200	>50	67 (32)[a]
<200	>50	49 (24)[a]

[a] Of individuals with a viral load greater than 50 copies/mL, 32 individuals were not receiving antiretroviral therapy at the time of viral load measurement.

Cohort studies such as the one we present herein are open to bias, with the possibility that patients in whom antiretroviral therapy is failing are lost to follow-up; we were unable to identify individuals who have transferred care, but reassuringly, the UK CHIC study has revealed that the number of transfers is very low.[6] In addition, we only studied 1 measure of resistance using 1 method. It is difficult to directly compare our study with the UK CHIC study because differing parameters were used to define triple-class resistance. In the UK CHIC study, triple-class resistance was defined as virological failure (>400 copies/mL during continuous drug use) of 3 subclasses of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and ritonavir-boosted protease inhibitors.

Factors that may have influenced the lower level of triple-class resistance may be the structured approach to antiretroviral prescription in our center. All naïve patients undergo baseline resistance testing before antiretroviral administration to review primary resistance. Individuals are seen by physicians in the "Treatment Advisory Clinic," where resistance test results are reviewed and therapeutic and trial options are discussed in full. Once the regimen has been constructed, individuals are seen in the "Start Clinic," where they are reviewed by a specialist HIV nurse and pharmacist. Within this forum, strategies are discussed to afford the patient the best chance of avoiding antiretroviral failure. Those thought to be intolerant of therapy or in whom therapy is failing are reviewed fully in the "Virtual Clinic," where resistance test findings and future treatment and trial options are discussed within the multidisciplinary team followed by intervention measures, such as input from adherence nurses.

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COMMENTS AND OPINIONS

Methotrexate Is Not Associated With Progression of Interstitial Lung Disease in Rheumatoid Arthritis

After carefully reading the article by Gochuico et al[1] on progressive preclinical interstitial lung disease (ILD) in rheumatoid arthritis (RA) in the January 28 issue of the *Archives*, we are concerned about the conclusions reached by the authors, namely that ILD is progressive in patients with RA, as the title of the article seems to indicate. If "progression" from subclinical to clinical disease is so frequent, we rheumatologists should be able to identify the clinical form more often than we do now. In fact, compared with years ago when the treatment of RA was much less aggressive than it is now, we saw extra-articular manifestations of RA in the lungs much more frequently than what we see nowadays. This perception is not unique to the United States or North America, where the cumulative incidence of pulmonary fibrosis after 30 years of follow-up in 609 patients from Olmsted County, Minnesota, was reported to be 1.9 per 100 in 2003.[2] For example, the frequency of pulmonary disease in 587 Italian patients with RA was reported to be 6.3% in 2000.[3] Finally, the statement about methotrexate use being a risk factor for ILD progression derives from unadjusted univariable analyses in which 9 of 12 patients who progressed to clinical ILD have been compared with 2 of 9 patients who had not progressed, with a *P* value that was significant ($P=.046$) but which became nonsignificant after Yates correction for small numbers on the 2×2 con-