HIV and Drug Resistance – Interpretation and Therapeutic Progress

The description of the clinical signs and symptoms of a new immunodeficiency syndrome, particularly in young man in 1981, was immediately followed by an urgent search for tools that might offer some hope to restore the capacity of the immune system or, if this was not possible, to terminate or delay the – at that time, deadly – process of destruction of this system. The causal agent was identified in 1983 – the retrovirus was initially named LAV(-1) or HTLV-III and later HIV-1 (human immunodeficiency virus). In 1987, the first specifically acting drug azidothymidine/zidovudine was licensed; it is still available on the market today. Due to frequent mutations and selection of the fittest drug-resistant HIV under this monotherapy, the therapeutic progress of this reverse transcriptase inhibitor after several months of treatment was only moderate. Further inhibitors of the reverse transcriptase were developed and licensed. The progress for most patients was only temporarily acceptable. A huge step forward in antiretroviral treatment was the introduction of the first protease inhibitors in 1996 and non-nucleoside reverse transcriptase inhibitors in 1997. Both groups of substances in combination with the nucleoside reverse transcriptase inhibitors worked well but when their efficacy weakened, the people involved in treatment and laboratory analysis were forced to routinely sequence part of the HIV-RNA genome for those mutations that change the key amino acids within the enzymatic pocket, drug-binding site and/or target-binding site.

Initially, a phenotypic assay for the analysis of antiretroviral drug resistance was developed and favored. This assay ultimately had several limitations, since not only the virus, the amplified or cloned part of the HIV genome was needed, but also all antiretroviral substances in a buffer-soluble form and partially modified as triphosphates, depending on the cells used. These assays worked well and provided an insight into the velocity and extension of drug resistance, but were finally stopped in routine analysis due to a high workload, drug substance shortage and the delay until a result would become available.

Experience from the determination of phenotypic resistance led to the identification and definition of specific key amino acids for the nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. While interpretation in reverse transcriptase inhibitor mutations was structured and unsophisticated, the mutations in the much shorter molecule of the protease were more complex and demanded an assisted interpretation program. Interpretation was simultaneously complicated by the subtypes of HIV-1 group M spreading in Europe, in which some of the amino acid positions displayed natural polymorphisms which lead to drug resistance or reduced drug susceptibility.

Meanwhile, in 1990, huge, freely accessible databanks like that in Los Alamos, N. Mex., USA, were established.

This enabled a comparison of individually obtained nucleic acid sequences with those deposited in the data bank. Another bank, working efficiently from the beginning and continuously improving, was that at Stanford University, Calif., USA. One of the chapters in this supplement describes their most recently developed interpretation methods. In Europe, taking into account the flaw of drug failure and being confronted with the deterioration of the health status of patients carrying divergent African HIV-1 (and additionally HIV-2), the first nationally developed interpretation algorithm became available in France (ANRS), followed by an independent installation in Belgium (REGA) and besides others finally one in Germany (geno2pheno and HIV-GRADE). The basics of these assays and the access to these programs via the Internet are described in this supplement. All the programs, including that from Stanford, remain available free of charge. Interpretation of all mutations was implemented on a data-algorithm-based interpretation and feedback system, including the analysis of feedback of the clinical data of both successful and unsuccessful courses of treatment from several European countries and studies like EuResist and RESINA. The management of these data volumes, their continuous refinement and extension and supplementation, over a few years, with information obtained by pyrosequencing could only be covered by individuals with a deep insight into data handling and biologically significant knowledge. Two chapters deal with this particular field.

A commercially accessible program was first introduced in Europe and later extended to North America. It was constantly improved upon and the nucleic acid sequence data was adapted to a virtual phenotype, thus covering the advantages of both phenotypic and genotypic resistance determination. One of the chapters lays down the basics of this program and the links for its interpretation.

Designing new drugs allowed a further step forward in the treatment of HIV-infected patients. Fusion inhibitors and entry inhibitors became available in 2003 and an integrase inhibitor in 2007. All the established drug resistance interpretation algorithms could easily be extended to the action and failure of these new drugs. This under-

lines the solidity and broad understanding of biological and computing connections of these algorithms.

HIV-2 has a different distribution across the world, a reduced pathogenicity and also a very divergent amino acid composition of the antiretroviral drug target sites. In HIV-2, the number of patients is lower than that of HIV-1 group M and only some of the antiretrovirals developed for HIV-1 are satisfactorily active. This delayed the interpretation of the key amino acids and the drug-failure-related clinical outcome. However, this interpretation is now available as well and is described in a special chapter in this volume. It will be a helpful tool in the treatment of HIV-2-infected patients.

Treating HIV- and HBV (hepatitis B virus)-coinfected patients presented clear evidence that the majority of the HIV reverse transcriptase inhibitors are also efficient HBV polymerase inhibitors and that permanent reduction of HBV replication can only be achieved by avoiding mutations that lead to HBV drug resistance. The systems and algorithms developed for HIV were easily adapted to the new challenge for HBV, demonstrating again the power of these established interpretation programs. A chapter with the interpretation of mutations occurring in the HBV genome is not included in this supplement, neither is coverage of the progress made by the development and availability of the HCV (hepatitis C virus) genotype 1 protease inhibitors and their resistance interpretation. But the programs and algorithms developed for HIV-1 are sufficiently robust to shift acquired knowledge for the interpretation of HBV und HCV mutations, again confirming the attractiveness and cleverness of the procedures described in this volume.

Putting these chapters together was a pleasure and it is the hope of all the authors that the knowledge we have shared will be a contribution for the benefit of HIV-infected patients, an appeal to develop new drugs and a step forward in the understanding of the close connections between biology, disease and computing analysis.

The author wishes to express his gratitude to his co-editors Rolf Kaiser and Martin Stürmer and all the contributors.

Lutz Gürtler, Munich