Letter to the Editor

ART FAILURE AND STRATEGIES FOR SWITCHING ART REGIMENS IN EUROPE

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The introduction of combination antiretroviral therapy (cART) represents a major turning point in the response to the HIV/AIDS epidemic. WHO European Region Member States have made significant progress in scaling up access to such treatment. By mid-2007, cART was available in the public sector health services in every country of the Region except Turkmenistan, with coverage estimated as very high (more than 75% of those in need of treatment) in at least 38 out of 53 Member States (1).

Though countries in eastern Europe and central Asia[1] have initiated the delivery of standardized first-line antiretroviral therapy (ART), as recommended by WHO, several key issues in the clinical management of patients remained unresolved as there has been no consensus among experts on a number of issues including: how virological failure to cART is defined; what HIV-RNA threshold level constitutes virological failure; what constitutes an early or late switch when cART no longer completely suppresses viral replication and what impact each has on the spread of drug-resistant (DR) HIV; when is the optimal time to switch to ART in case of a lack of complete viral suppression; and what role resistance testing of HIV has in determining when to switch and which treatment regime to switch to.

WHO's public health approach to cART is first and foremost to extend life, and then to have one evidence-based global standard for using cART. This consists of one first-line cART regimen. If this fails, one second-line cART regimen is employed (then salvage cART if available); utilisation of three orally available drug classes; simplicity of drug combinations (including fixed-dose combinations); straightforward recommendations for switch timing and toxicity substitutions; consideration of the availability of and access to laboratory monitoring; and standard population-based HIV DR monitoring and surveillance. Recommendations that are meant for all settings, globally, may appear to be nominal. Consequently, many middle- and high-income countries that have more resources and better infrastructure are following clinical guidelines that are individually tailored, initiate treatment earlier, allow a greater variety of drug combinations to be used, and recommend more extensive laboratory monitoring of treatment outcomes.

The WHO Regional Office for Europe convened European HIV/AIDS treatment experts for a technical consultation to review current practices in the WHO European Region and to develop a consensus around these unresolved issues. The experts reviewed international HIV/AIDS treatment guidelines and found scant evidence on most of the issues.[2]

CURRENT EVIDENCE

The ART guidelines reviewed, including evidence used by western European countries, are similar in terms of defining treatment goals, failure and optimal time for switching regimens. All guidelines use viral load (VL) measurement as the key indicator for switching cART regimens, even though the end-points differ. Countries also differ in strategies used when virological failure of cART is suspected. All guidelines recommend HIV DR testing for all patients suspected of cART virological failure (2–4). In western Europe, the proportion of cART patients achieving undetectable VL ranges from 50–90% (5) with increasing trends

[1] For the purpose of this article, the countries being referred to in eastern Europe and central Asia are: Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, the Russian Federation, Tajikistan, Ukraine and Uzbekistan.
[2] The full report of the meeting on which this article is based can be found at http://www.euro.who.int/aids.

over time. The goal of cART is to reach undetectable VL within six months of starting therapy and to maintain this status for the rest of the patient's life. This requires uninterrupted provision of effective cART and a high level of treatment adherence.

Evidence shows that cART assists patients in raising CD4 counts and decreasing VL. If VL is kept undetectable, then CD4 counts continue to increase over the years until they reach almost normal levels (6–8).

Many studies support the notion that patients who are kept on failing regimens accumulate more viral mutations than those whose regimens are changed immediately upon the diagnosis of virological failure. This occurs irrespective of the type of regimen, provided it contains drugs with a genetic barrier higher than 1 (i.e. thymidine analogues and protease inhibitors – PIs) (9–14).

There is some evidence that resistance testing should guide treatment change; several randomized studies show a moderate and short-term effect on treatment outcome of DR testing in virologically failing patients (15–19), others show no significant effect at all (20–22). Most of these studies were conducted several years ago, are relatively small and may not apply to current cART or current algorithms for interpreting DR testing. A continuing problem with DR testing studies is that by the end of the study, results may no longer be applicable because new drugs, technology and mutational patterns develop over time.

Drug resistance is common among treated patients in western Europe because of earlier availability and long use of mono and dual therapy before triple therapy became available in the mid-1990s. This resistance can usually be managed by second- and third-line therapies leading to renewed complete viral suppression. While individual DR testing may not benefit every single patient, studies suggest that it is cost-effective when used as a part of managing virological failure. Additionally, testing algorithms and other knowledge continuously improve and most experts agree that it should be an integrated part of a comprehensive HIV care programme and part of routine HIV care in Europe. Arguments against routine individual resistance testing include the high cost, difficulty to obtain alternative drugs (making the relevance of the testing questionable), difficulties to perform DR testing if HIV-RNA level is low (e.g. <1,000 copies/ml), and the importance of minority variants that might be missed by standard testing.

HIV TREATMENT AND CARE SERVICES IN EASTERN EUROPE AND CENTRAL ASIAN COUNTRIES

HIV epidemics in eastern Europe and central Asia occur mostly among injecting drug users and their sexual partners and fall into the range of low-level or concentrated epidemics, with a manageable number of people living with HIV (PLHIV) in need of treatment (23).

HIV/AIDS treatment and care services are provided exclusively by public health systems on an out-patient basis through AIDS centres or polyclinics, which exist in major urban areas. In-patient treatment is either provided in infectious disease hospitals or units in general hospitals. Specialized HIV services work as primary health care facilities. Usually, no referral is needed, there are no waiting lists, and services are free of charge. Once HIV diagnosis is established, territorial AIDS centres register PLHIV, who become eligible for continuous treatment and care free of charge. There is no lack of physicians, but there may be a lack of capacity and an unequal distribution of physicians (countries´ unpublished communications, December 2007). From 6–30% of PLHIV under care are presently on cART (23).

All countries provide regular, free-of-charge CD4 and VL testing to patients with HIV. Belarus, Georgia and the Russian Federation have also started DR testing of individual patients who fail cART regimens (countries´ unpublished communications, December 2007). Six (Armenia, Belarus, Georgia, Moldova, the Russian Federation and Ukraine) out of the eleven countries questioned use both VL and CD4 criteria in determining ART failure. Four countries in central Asia use only CD4 count, as VL has only become available very recently. Although these are the currently available laboratory capabilities, their use for all patients under treatment varies in each country.

All countries providing cART follow WHO recommendations for first-line regimens, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and a range of PIs; only Kyrgyzstan and Tajikistan are limited to one PI, LPV/r. Georgia and the Russian Federation also have fusion inhibitors for future treatment options. In the Russian Federation and Ukraine, first-line cART with boosted PIs, particularly with LPV/r is also popular.

CONSENSUS AND RECOMMENDATIONS

Based on an examination of the evidence, expert presentations and deliberations during the consultation, regional consensus was achieved on the goal of ART, the definitions of first- and second-line virological failure, when to switch and the minimum monitoring requirements of VL and CD4 for ART patients.

Goals of ART

The goals of ART are to maximize life expectancy (to that of normal life expectancy) and quality of life; minimize the risk of drug resistance and toxicity; and reduce the risk of HIV transmission.

Definition of First-line Failure

The definition of first-line failure is based either on virological failure or immunological failure (CD4), if VL testing is not possible. Basing ART failure solely on clinical grounds is considered a suboptimal approach; countries are encouraged to ensure that at least regular CD4 monitoring is in place. Poor adherence issues and drug interactions need to be ruled out before failure is confirmed.

There are two scenarios of *virological failure*: primary virological failure – no response by patient, i.e., VL does not decrease to <50 copies/ml on two different occasions after more than six months of cART, and secondary virological failure – viral rebound, i.e., VL >50 copies/ml confirmed.

Immunological failure is defined as a 25% drop from the patient's maximum CD4 level or failure to increase CD4 cell count >50 cells/mm^3 during the first year of ART.

If the second-line regimen contains drugs that exclude the possibility of cross resistance of the first-line regimen the patient

is currently failing, then a resistance test is not necessary in order to make the switch.

Strategies for Switching ART Regimens

There are two major strategies for switching ART regimens, early and late switch. Early switch occurs when VL >400 (>50– <1,000)[3] copies/ml. Its advantages are the preservation of treatment options, higher likelihood of effective response, decreased risk of non-AIDS and AIDS related events. Disadvantages of early switch are high costs and more rapid exhaustion of ARV drug options and the need for routine VL laboratory testing.

The advantage of a late switch (VL ≥1,000–10,000 copies/ml or a 25% drop in CD4 count) is reduced costs. Disadvantages of late switching are the greater accumulation of resistance mutations and potentially enhanced transmission of resistant virus, it may compromise treatment response and also limit the choice of active ARVs for second-line therapy.

If at six months VL >50 copies/ml, the physician before switching to second-line treatment should assess and address adherence, drug toxicity (substituting the toxic drugs) and any drug interactions.

The long-term implications of these approaches are unknown and studies comparing the switch management approaches are urgently needed.

Minimum Monitoring Requirements

VL should be part of the standard of care of PLHIV and should be undertaken prior to initiation of cART and then at months 1, 3, 6 and 12; subsequent monitoring may be at longer intervals for patients responding well to treatment. Monitoring VL every 6–12 months is acceptable if there are local constraints on access or cost.

CD4 cell counts should be done prior to starting cART, then two to four times in the first year; subsequent monitoring may be twice annually.

Definition of Second-line Failure

The definition of second-line failure is the same as first-line failure (virological and immunological). Managing second-line failure differs depending on available drug options and greater use of resistance testing. New drug classes, for example entry inhibitors, should be introduced where possible.

Drug Resistance Testing

If HIV DR testing is not available after first-line failure, a blood sample should be taken and kept frozen in the event that second-line failure occurs; both blood samples, after first and second-line failure, should then be tested in deciding on a salvage regimen.

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[3] More than 50 copies, but less than 1,000 copies refers to the secondary definition of first-line failure, switching within this range of VL is an early switch.

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