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THE GLC MECHANISM

AN INNOVATIVE PUBLIC PRIVATE PARTNERSHIP UNDER THE UMBRELLA OF THE DOTS-PLUS WORKING GROUP

Introduction

After 4 years of piloting the programmatic diagnosis and treatment of Multi-Drug Resistant Tuberculosis (MDR-TB) through the Green Light Committee (GLC), this strategy (known as DOTS-Plus), has now been accepted as the standard of care for MDR-TB patients in low and middle income countries.

The comprehensive package of the GLC mechanism supports countries to integrate the diagnosis and treatment of MDR-TB within regular TB control programs. It combines:
1) increasing access to preferentially priced quality assured second-line drugs;
2) a review mechanism (the GLC) to ensure rational use of these drugs;
3) technical 'pre-approval assistance' and program monitoring and;
4) policy development (guidelines and research).

This background paper summarizes the status and the sustainability of the GLC mechanism, relevant developments, the challenges ahead and the need for close coordination and collaboration between the Stop TB Partnership Working Groups (WGs), more in particular the DOTS expansion Working Group (DEWG), its Lab Strengthening WG, the New Diagnostics WG and the DOTS-Plus WG. Concrete examples of collaboration are given below, under 'Plan of action'.

Relevant new information and developments

- ***Epidemiological information***

The Third Global Drug-Resistance Surveillance Report identifies new settings and countries with high levels of MDR-TB. Taking into account that most settings with poor TB control programs have not yet been surveyed, it is likely that many more unidentified high MDR prevalence settings exist.
Because the global map of drug-resistance is still very incomplete, the GLC secretariat collected additional programmatic data from important high burden countries, like Russia, the Former Soviet Countries (FSU), China, India and South Africa. These indicate very high proportions of retreatment cases among all pulmonary cases, ranging from 20-50%. As retreatment cases in general and failure cases in particular are at increased risk of multi or poly-drug resistance, this finding may indicate an important threat to TB control in these settings. Operational research in Vietnam shows that a significant proportion of 'chronic' cases survive and continue to transmit MDRTB to their contacts.

Although TB control history shows that DOTS introduction can reduce both the MDR-TB problem and the size of the retreatment cohorts, more recent experiences in FSU countries and Russia illustrate that this is not the case in settings where both problems are mixed above a certain threshold. In addition, the HIV epidemic and the extensive uncontrolled use of TB drugs create epidemiological situations which frustrate the expansion of 'regular' DOTS.

- ***Increasing momentum with politicians and tuberculosis experts***

The year 2004 is marked by two important decisions and shifting opinions

Firstly, in May 2004, following the World Health Assembly (WHA), the Executive Board of WHO has made important recommendations on sustainable financing of tuberculosis control. In a resolution the Executive board encourages countries to ensure that tuberculosis patients have access to the universal standard of care. In addition the Director-General is requested to ' implement and strengthen strategies for the effective control and management of persons with drug-resistant tuberculosis. This resolution will be debated by the WHA in May 2005.

Secondly, in June 2004, the Strategic and Technical Advisory Group (STAG) on tuberculosis has decided that the standard of care for MDR-TB patients is a category 4 (DOTS-Plus) regimen which is tailored to the individual drug-susceptibility results or to representative drug-resistance surveillance (DRS) data in that specific retreatment category. In the revised WHO treatment guidelines countries are encouraged to analyze the DRS data among retreatment categories, with focus on failure cases and to prepare for - and implement a category 4 regimen in MDR patients.

In addition tuberculosis consultants from different organizations and NTP managers are still confronted with barriers to introduce regular DOTS in countries with high levels of MDR, such as FSU countries and Russian oblasts. There is increasing momentum to move from 'DOTS first' to simultaneous introduction of an integrated DOTS/DOTS-Plus model.

Lastly, evidence collected by the GLC secretariat shows that second-line drugs of unknown quality are produced in many high burden settings and are widely (mis)used throughout the world. Partners who used to think that DOTS-Plus was too expensive, start recognizing that DOTS-Plus means shifting of funds from inadequately used poor quality second-line drugs to the rational and less expensive use within the context of a DOTS program.

- ***Important developments related to the GLC mechanism operations***

Since its creation in 2000, the GLC mechanism has faced many challenges and has redirected its operations accordingly. Achievements and developments include the following:

1. After 4 years of GLC operations and policy-development, DOTS-Plus moves from pilot-phase to routine implementation. In most projects full integration with the regular DOTS program has already been achieved or is underway. The GLC experiences show that the DOTS-Plus component needs to be tailored to the setting within a framework of essential conditions (which are being described in the revised DOTS-Plus guidelines).

2. The GLC is confronted with a sharply increasing demand for technical assistance and policy development. This is mainly due to the decision of the Global Fund for AIDS, Tuberculosis and Malaria (GFATM) to select the GLC mechanism to review, approve, monitor and procure all GFATM projects with a DOTS-Plus component. This linkage of the GLC mechanism with a global funding mechanism meant a major boost to the expansion of DOTS-Plus worldwide. Undisputedly the GFATM allows countries to overcome financial barriers and facilitates the integration of DOTS-Plus components into regular DOTS programs. At the same time, the GFATM saves large amounts of money through the GLC mechanism. Based on the number of GFATM approved DOTS-Plus

patients by August 2004 (18 projects), minimum $66 million are saved if compared to purchase of the same amount of (non-quality assured!) drugs in low income countries.

3. GLC related DOTS-Plus expansion continues to accelerate. By August 2004, 25 projects were approved worldwide, covering 8,193 MDR patients. Most projects start with small cohorts and we expect the majority will apply for cohort expansion in the near future. Current estimates indicate that in 2005, over 5000 new patients will be added. Since its creation the GLC committee has held 25 meetings, reviewed 38 applications, organized 20 pre-approval technical assistance missions, organized 14 monitoring missions and 2 drug-management courses. Currently, 11 applications are under review, whereas another 9 applications are being prepared. Based on the action plan for 2005 (see later), a further acceleration is anticipated.

4. Preliminary data from three GLC sites show that DOTS-Plus is feasible and (cost) effective under routine DOTS-program conditions in mid- and high prevalence countries. Moreover, there is increasing evidence that the introduction of DOTS-plus components results in strengthening of the regular DOTS-program and laboratory capacity.

5. The first pilot projects were situated in the so called hot MDR-TB 'hot spots' and were heavily supported by external agencies, both technically and financially. However, this situation has changed remarkably. The diagnosis and treatment of MDR-TB is more and more regarded as a routine objective, resulting in applications from countries with a limited MDR-TB problem, such as Tanzania (application under preparation). These countries require intensive technical assistance, as usually there is no involvement of an external technical partner. In the same time, these settings can use relatively cheap standardized DOTS-Plus regimens (<$500) because there is no resistance to second-line drugs.

6. The DOTS-Plus guidelines are under revision. The new guidelines will be based on the consensus within the GLC committee (IUATLD, PIH, WHO, CDC, Baltic combination) and the experiences and evidence from the GLC projects.

Challenges ahead

Despite (and ironically due to) the increased technical, political and financial momentum, the GLC mechanism is facing serious challenges:

Increasing demand for technical assistance and coordinating activities at secretariat level

- Lack of sufficient consultant capacity at the international level
- Lack of DOTS-Plus expertise and experience at the regional and country level;
- The GFATM funding mechanism requires intensified pro-active technical support;
- With an increasing number of applicants and approved projects (also outside the GFATM) the need for GLC assessment and monitoring missions sharply increases;
- The secretariats of the DOTS-Plus WG and the GLC lack sufficient staff to adequately coordinate the DOTS-Plus Partnership activities (training, technical

assistance, collaboration with other WGs, drug-procurement and policy-development.

Laboratory capacity

- Lack of laboratory capacity forms a major (and often the only) barrier to the expansion of DOTS-Plus and drug resistance surveillance.
- Lack of laboratory consultant capacity;
- The need to facilitate the bacteriological diagnosis and monitoring of drug-resistant tuberculosis.

Global production and (mis)use of non-quality assured second-line drugs

- Efforts to identify second-line drug producers and drug-resistance data from GLC projects illustrate that expensive non-quality assured second-line drugs are being misused world-wide This situation leads to amplification of (second-line) drug-resistance and continued transmission of MDR-TB strains.
- The ultimate challenge is to shift funds from the uncontrolled (mis) use of expensive low quality second-line drugs to the rational use of quality controlled second-line drugs in the context of a DOTS program.

Drug procurement

- Uninterrupted and timely supply of quality assured second -line drugs;
- Identifying and mobilizing manufacturers for prequalification;
- Rapid establishment of a white list of quality assured second-line drugs, while preventing a monopoly for these drugs.

Current and future financial constraints

- The current funding available for DOTS-Plus coordination and the operations of the GLC mechanism is not sufficient to meet the existing and future challenges listed above. The funding gap results in delays to address the challenges listed above;
- The GLC mechanism is currently funded by the Gates Foundation, USAID and Eli Lilly. In addition, the Stop TB Partnership supports the functioning of the DOTS-Plus WG. With the Gates funding ending July 2005, it's the future of the GLC mechanism that is at stake.

Plan of action

The activities are described in relation to the essential elements of the GLC mechanism and relate to the challenges listed above. All activities are coordinated by the GLC secretariat, in close collaboration with the GLC member institutions, the Core Group of the DOTS-Plus WG and the Drug-Resistance team within WHO.

Human resources and technical assistance

Obviously, integrating DOTS-plus components into DOTS programs requires close collaboration with the activities of the DEWG. During the DEWG meeting in Paris a 1,5 hour time slot will be devoted to this subject. Concrete activities include:

- Training of DOTS consultants working with Stop TB Partner institutions, adding a DOTS-Plus component to their expertise;
- Organization of DOTS-Plus training courses at the country and regional level;
- Identification of - and pro-active technical assistance to countries eligible for GFATM funding, ensuring that DOTS-Plus requirements (laboratory capacity, drug-resistance surveillance, technical assistance and program design) are adequately covered in the GFATM application;
- Integrating GLC monitoring missions in regular DEWG program review missions;
- Joint DOTS/DOTS Plus pre-approval assistance missions to countries preparing GLC applications;
- Technical assistance aiming for integration of DOTS-Plus components in country TB control development plans (in close collaboration with partners involved in DOTS-expansion);
- Integrate targeted DOTS-Plus assistance to countries at increased risk of MDR, such as China and Russia, in regular country review missions;
- Organization of drug-management courses focusing on second-line drugs;
- Linking DOTS-Plus technical assistance with DOTS expansion.

Laboratory capacity

- To promote the incorporation of laboratory capacity-building in GFATM proposals and country TB developments plans;
- To collaborate closely with the laboratory strengthening sub-group of the DEWG, ensuring that this sub-group addresses the lack of culture- and drug-susceptibility testing capacity ;
- To intensify collaboration with the New Diagnostics WG, by field testing of (novel) diagnostics within the controlled environment of the GLC approved pilot projects.

Access to quality assured second line drugs

- Completing the list of second-line drug manufacturers and inviting them to participate in the prequalification program, thus ensuring a sufficient and competitive market. A meeting with manufacturers and prequalification specialists is organized for that purpose;
- Introduction of software to track the status of drug procurement in GLC projects;
- Prequalification of second line drugs and manufacturers;
- Establishment of a white list of quality assured second-line drugs;
- Quality testing of batches of drugs supplied through the GLC.

Review mechanism

- Introduction of software which facilitates the monitoring of the status of projects;
- financial compensation of the GLC member institutions;
- The operations of the GLC secretariat: convening review meetings, communication with approved projects and potential applicants, communication with the GFATM, coordination of technical assistance.

Policy-development

- Production and distribution of the revised DOTS-Plus guidelines (due Dec 2004);
- Continued (case-based) data-collection from GLC projects;
- Operational research;
- Collaboration with FIND.

Sustainability of the GLC mechanism

With the Gates grant ending in July 2005, the sustainability of the GLC is at stake. Already in 2005, the GLC mechanism is confronted with a $900,000 funding gap.

The GLC secretariat and the GLC member institutions are in the process of developing a mid/long term business plan, covering all essential elements of the GLC mechanism, including drug-resistance surveillance. After endorsement of the plan by the current partners and GLC member institutes, the plan will serve as a tool for resource mobilization. The overall aim is to involve a larger group of donors, thus limiting the risks of donor dependency and increasing the ownership for DOTS-Plus within the donor community. The GLC partners (CDC, IUATLD, PIH, WHO, the NTPs of Estonia and Latvia) trust that this business plan will be incorporated in the TBP resource mobilization plan.

A first modest draft GLC business plan indicates that at least $5 million is required to cover GLC mechanism operations in the period 2005-2008. This estimate includes the functioning of the GLC and DOTS-Plus WG secretariats, technical assistance, monitoring, training, pre-qualification of second-line drugs and operational research. However, drug costs, laboratory capacity building and fee for consultants are not yet included.

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