MESA: VIH

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Innovaciones en la epidemiología molecular del VIH y la TB

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La epidemiología molecular puede definirse de muchas maneras. Una de ellas es el uso de la información genética del patógeno para entender los patrones de transmisión de una enfermedad. Por lo tanto, la epidemiología molecular es una disciplina que complementa los estudios epidemiológicos con implicaciones en la identificación de brotes, de patógenos desconocidos o de dinámicas poblacionales de transmisión. Dado su dependencia de los métodos moleculares, la epidemiología molecular ha ido evolucionando con el desarrollo de nuevas técnicas para interrogar el genoma del patógeno. De esta manera, los métodos de tipificación han ido evolucionando desde aproximaciones poco escalables, como fueron los geles de electroforesis de proteínas, a métodos que permiten el procesado de un gran número de muestras, y que generan un gran número de datos genéticos en un espacio de tiempo relativamente corto.

Desde hace pocos años se han ido incorporando las nuevas tecnologías de secuenciación genómica al diagnóstico, tipificación y epidemiología de patógenos como virus, bacterias y hongos[1]. ¿Qué es lo que hace diferentes a dichas tecnologías? En el caso de virus y bacterias nos permite acceder al genoma completo del patógeno a un precio mucho más asequible. Hasta ahora todos los métodos usados interrogaban regiones muy pequeñas de los genomas, en muchos casos esas regiones no representaban ni el 1% de los nucleótidos de un genoma. Por lo tanto, en muchas ocasiones, la resolución de las relaciones entre las variantes circulantes era limitada, lo que a su vez limita la identificación de patrones de transmisión. Por el contrario, el uso de genomas completos nos permite una resolución no alcanzada antes. Además, tiene la ventaja de que podemos identificar todos los cambios genómicos ocurridos en la población estudiada y, como tal, tener una primera idea de las bases biológicas que puedan ser relevantes para la infección y transmisión de un patógeno. ¿Qué ha cambiado en dichas tecnologías con respecto a la secuenciación Sanger convencional? Hace catorce años, el primer genoma bacteriano fue secuenciado. Dicho genoma era el de *Haemophilus influenzae* y tardó más de un año en completarse y costó millones de euros. Hoy en día podemos secuenciar en menos de una semana cientos de genomas de cepas de *H. influenzae* y a un precio de menos de 100 euros por cepa. Por lo tanto, lo que ha cambiado es la escala de los datos que somos capaces de generar. ¿Qué implicaciones tiene para salud pública? El abaratamiento de los costes de secuenciación genómica permite usar el genoma completo en tres campos esenciales de salud pública: diagnóstico, identificación de brotes y dinámicas de transmisión. Uno de los mejores ejemplos son los avances en la epidemiología y diagnóstico de la tuberculosis.

El uso de genomas completos para identificar y estudiar brotes de tuberculosis empezó en 2011. Gardy *et al.*, 2011[2] fueron capaces de resolver un brote de tuberculosis que se remontaba a principios de los años 90. Combinando la información genómica de los aislados bacterianos, los datos epidemiológicos y los datos de interacciones sociales, los autores demostraron que se puede obtener una mayor resolución de los eventos de transmisión ocurridos dentro del brote. De esta manera, desde 2010 la secuenciación genómica se ha estado usando para resolver brotes, que se han mantenido a lo largo de décadas[3] y, en otros casos, para identificar procesos que se desconocían asociados a un brote[4].

Además de para brotes específicos, los genomas completos nos permiten estudiar las dinámicas poblacionales y epidemiológicas de *Mycobacterium tuberculosis*. En comparación con marcadores MIRU-VNTR, los genomas completos consiguen una mejor delimitación de los grupos de transmisión, así como una mejor resolución de "quién ha infectado a quién". Sin embargo, el análisis primario y secundario de los datos de secuenciación no es simple y requiere de experiencia bioinformática. En la Comunidad Valenciana estamos desarrollando nuevas aproximaciones para reconstruir los eventos de transmisión, a partir de los datos de los genomas de una gran parte de los aislados obtenidos en los hospitales de la región. Dicha información será transmitida y complementada con los datos epidemiológicos, microbiológicos y demográficos del paciente e integrados en los sistemas de información sanitaria de la *Conselleria de Sanitat de la Comunitat Valenciana*. El objetivo es evaluar la contribución de la epidemiología genómica a un mejor control de la tuberculosis, bien porque permita identificar nuevos focos de transmisión, bien porque permite evaluar las aproximaciones de control epidemiológico existentes.

A la vez que información epidemiológica, la determinación de la secuencia genómica nos está también informando simultáneamente de la presencia de mutaciones asociadas a resistencias a antibióticos. Por lo tanto, el genoma completo también es una herramienta diagnóstico. De hecho, hay que destacar que en el Reino Unido se va a implementar la secuenciación genómica como herramienta diagnóstica en los hospitales ingleses, después de demostrar que es una aproximación coste-efectiva[5]. Sin embargo, tanto a nivel epidemiológico como a nivel diagnóstico, la gran barrera sigue siendo la dependencia de un cultivo positivo. Si fuéramos capaces de obtener el genoma completo a partir de muestra diagnósticos reduciríamos el tiempo de espera de diagnóstico de resistencias y de epidemiología de semanas (o incluso meses) a días. Ese futuro aún no está aquí, aunque hay muchos laboratorios en el mundo que están trabajando en ello. Mientras el futuro llega, debemos explorar las ventajas, pero también los desafíos que representa la secuenciación genómica como herramienta en la epidemiología y diagnóstico de la enfermedad.

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Actualización del documento de consenso de GESIDA sobre tratamiento de la TB en los pacientes con infección por VIH

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La generalización del tratamiento antirretroviral (TAR) y su elevada eficacia en el control de la replicación viral, facilitando la recuperación inmune, se ha relacionado con una importante disminución de la incidencia de tuberculosis (TB) en los pacientes con infección por VIH. No, así obstante, la incidencia en esta población sigue siendo elevada y persiste un mayor riesgo de fracaso terapéutico y de mortalidad. En un reciente análisis de la cohorte española prospectiva CoRIS, con 6.811 pacientes con infección por VIH (17.004 pacientes-año de seguimiento), la incidencia de TB oscila entre 12,1 y 14,1 por 1.000 personas-año[1],

lo que supone una incidencia más de 100 veces superior a la de la población general en España (10,8 por 100.000)[2].

Las bases del tratamiento de la TB en pacientes coinfectados son, en esencia, similares a las de la población general, utilizándose las mismas combinaciones de fármacos con el propósito de erradicar las diferentes poblaciones bacilares y evitar la aparición de resistencias secundarias. Sin embargo, la presencia de la infección por el VIH confiere a este tratamiento algunas peculiaridades, fundamentalmente derivadas de la posible inmunodeficiencia asociada y de la interacción con el TAR, que obligan a realizar consideraciones y recomendaciones específicas.

Con objeto de facilitar el manejo y el tratamiento de los pacientes con coinfección TB-VIH en España, el Grupo de Estudio de Sida (GESIDA) de la Sociedad Española de Enfermedades Infecciosas (SEIMC) junto con el Plan Nacional sobre el Sida elaboraron en 2013 un documento de recomendaciones para el tratamiento de la tuberculosis en personas infectadas por el VIH, dirigido a todos los profesionales que atienden o que en algún momento puedan atender a pacientes con infección por el VIH[3].

Desde entonces, algunas nuevas evidencias en este campo (fundamentalmente en lo referente al momento óptimo para iniciar el TAR en personas con diagnóstico simultáneo de TB y VIH, la disponibilidad de nuevos antirretrovirales que facilitan el tratamiento conjunto de ambas infecciones o la evolución de la epidemia de tuberculosis multirresistente y extremadamente resistente) han hecho aconsejable una actualización del documento, que será publicada próximamente.

Como líneas generales, se debe recordar que todos los pacientes con tuberculosis e infección VIH deben recibir TAR simultáneamente con el tratamiento antituberculoso, demorándolo de 2 a 8 semanas tras el inicio del tratamiento antituberculoso, en función de la situación inmunológica del paciente, para evitar complicaciones y facilitar la adherencia y tolerancia. La irrupción de los inhibidores de integrasa como fármacos preferentes en el TAR de inicio por su mayor eficacia y tolerancia obliga a considerarlos también en los pacientes con TB y VIH. Tanto raltegravir como dolutegravir (duplicando la dosificación habitual) son opciones ventajosas a considerar en este escenario. Respecto al tratamiento antituberculoso, en estos pacientes se debe administrar a diario, al menos durante la fase de inducción, no recomendándose en ningún caso las pautas administradas 2 veces por semana, que están absolutamente contraindicadas en pacientes con recuento de linfocitos CD4 < 100/ul). Además, la duración del tratamiento de la TB pulmonar susceptible debe prolongarse hasta los 9 meses en pacientes con bajo recuento de linfocitos CD4+ en los que no se prevea una respuesta inmunológica adecuada, y en los pacientes en los que no se pueda asegurar una toma adecuada de todas las dosis prescritas.

Los pacientes con TB y VIH también tienen un riesgo elevado de empeoramiento paradójico de los síntomas y manifestaciones de la TB tras el inicio del tratamiento anti-TB y del TAR. Este cuadro, conocido como Síndrome Inflamatorio de Reconstitución Inmune (o IRIS, por sus siglas en inglés), debe ser reconocido y manejado adecuadamente para evitar cambios innecesarios de tratamiento.

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Multidrug-resistant (MDR)-TB in HIV-infected children

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The global burden of tuberculosis in children is approximately 850 000 - 1 million cases per year; of these, 25 000-30 000 have multidrug-resistant tuberculosis (MDR-TB; i.e. resistance to at least isoniazid and rifampicin)[1]. It is not clear from the literature whether MDR-TB occurs more often in HIV-infected children than in HIV-uninfected children. However, in a cohort of >1700 culture-confirmed cases with known HIV status we found significantly more MDR-TB and rifampicin mono-resistant (RMR)-TB cases, but not isoniazid mono-resistant TB cases amongst children with HIV infection (HS Schaaf - unpublished data).

The challenge in HIV-infected children is to think of TB in the differential diagnosis and clinically distinguish TB from other conditions associated with HIV disease. If TB is suspected, specimens should be obtained from the children for microbiological confirmation before starting treatment. Although MDR-TB is a microbiological diagnosis, microbiological confirmation in children is often not possible therefore the diagnosis is made as follows:

- Confirmed if an MDR *M. tuberculosis* strain is isolated from a child.
- Probable MDR-TB if there is known contact with an infectious adult DR-TB case (>78-90% concordance in several studies).

Table 1. Different drug groups, currently recommended paediatric doses and cerebrospinal fluid penetration of the antituberculosis drugs.

MDR-TB Drug Groups	Recommended daily paediatric dose (once daily doses unless otherwise indicated)
Group A. Fluoroquinolones	
– Levofloxacin	15-20 mg/kg
– Moxifloxacin	10 mg/kg
Group B. Second-line injectable agents:	
Amikacin, kanamycin & capreomycin	18-20 mg/kg
Group C: Other core drugs	
– Ethionamide	15-20 mg/kg
– Terizidone/cycloserine	15-20 mg/kg
– Clofazimine	2-5 mg/kg (5-10 kg: 50mg alternative days; 10-20 kg: 50mg/day; >20 kg: 100mg/day)
– Linezolid	<10 years: 10mg/kg twice daily >10 years: 300-600 mg daily
Group D1: Add-on drugs	
– INH high-dose	15-20 mg/kg (max 400mg)
– Ethambutol	20-25 mg/kg
– Pyrazinamide	30-40 mg/kg
Group D2: New drugs	
– Delamanid	> 6yrs and >20kg: 50 mg twice daily > 12yrs and >35kg: 100 mg twice daily Currently no dose for younger children
– Bedaquiline	> 12 years and >33kg: 400mg daily for 2 weeks followed by 200mg 3 x/week for 22 weeks Currently no dose for younger children
Group D3: Other add-on drugs	
– Para-aminosalicylic acid (PAS)	150-200 mg/kg as single or divided daily dose
– Amoxicillin-clavulanate with meropenem or imipenem	20-30 mg/kg 8-hourly with meropenem/imipenem at bacterial doses

– Possible MDR-TB if a child gets worse on treatment, failing adherent treatment or if an adult source case who has no drug susceptibility test (DST)-result is a treatment failure, a retreatment case or died of TB during adherent treatment.

Both genotypic (Xpert MTB/RIF and line probe assays as well as gene sequencing) and culture and DST is used for microbiological diagnosis, with the advantage of genotypic tests of being more rapid, but cultures are still the gold standard and provides the opportunity for wider range of DSTs to be performed

Treatment of MDR-TB is "rapidly" changing: the armamentarium of drugs are increasing with repurposed drugs (e.g. linezolid, clofazimine and meropenem/amoxiclav) and new drugs (delamanid and bedaquiline) being added. The WHO have recently reorganized the different drug groups to include these and also introduced a 9-12-month shortened regimen for RMR or strictly MDR-TB cases, including children and HIV-infected patients[2].

There are multiple challenges in managing children with MDR-TB and HIV: Antiretroviral therapy (ART) and MDR-TB treatment are given together – often with additional supplements and treatment of other conditions. This leads to children receiving many drugs, which could have similar drug adverse effects; drug-drug interactions may occur (although not as prominent as with the rifamycins); child-friendly formulations of second-line anti-TB drugs are rarely available; and currently almost all children co-infected with MDR-TB/HIV still receive a daily second-line injectable agent causing adverse events and administering problems (IV or IM). Pharmacovigilance is needed to identify adverse events of the anti-TB drugs during treatment[3,4].

Last but most important are attempts to prevent MDR-TB in child contacts of MDR-TB cases[5]. The opinion is swinging in favour of preventive therapy although there is much debate about the optimal regimen; however, careful follow-up remains essential in all contacts to identify development of disease early and provide appropriate therapy.

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The Global Fund Support to fight Tuberculosis and TB/HIV

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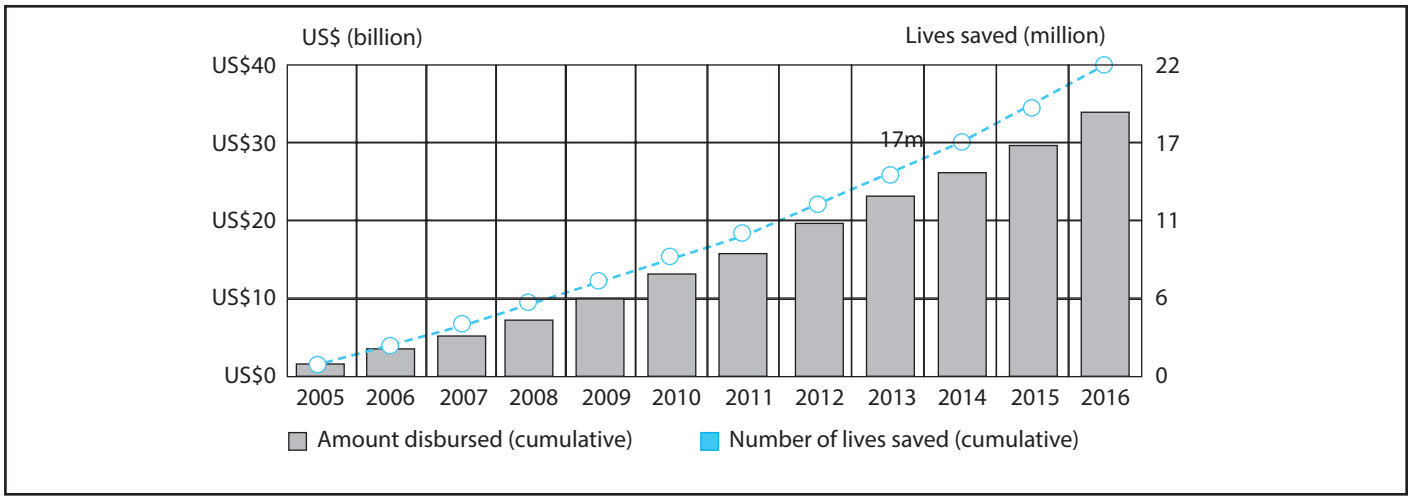
Background

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GF) was created in 2002 to raise, manage and invest the world's money to respond to three of the deadliest infectious diseases, such AIDS, Tuberculosis and Malaria. The GF is a partnership organization that brings together finances, technical expertise, the experience and knowledge of communities affected by the diseases, innovation and a capacity for constant evolution. The partners come with diverse abilities and points of view, but with the common aim to serve people, to strive for social justice, and to achieve impact against the three diseases - and ultimately end the epidemics.

The GF raises and invests nearly *US$4 billion a year* to support programs run by local experts in countries and communities most

Figure 1. Number of Lives Saved Through Global Fund-Supported Programs.



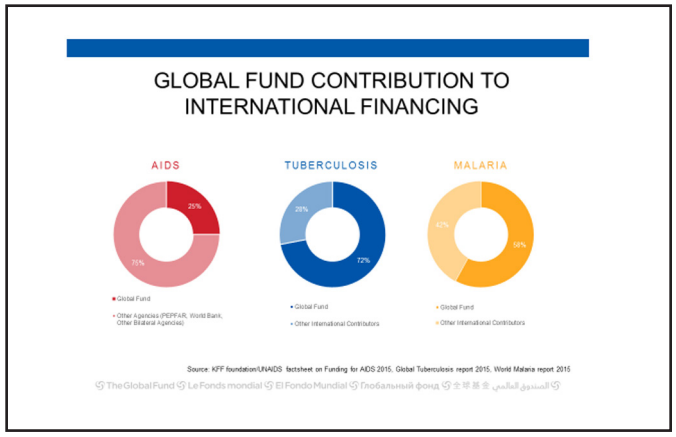
in need. As part of the principles of the GF approach, countries' ownership is an essential component, which means that people implementing programs on the ground determine their own solutions to fighting the three diseases - tailors its response to the political, cultural and epidemiological context - and take full responsibility for them.

The GF investment in health programs has grown steadily, and as of July 2016, it had disbursed *US$30 billion* to support country programs and this has contributed to: save *20 million lives saved and decline* of *one-third* in the number of people dying from HIV, TB and malaria.

In countries where the Global Fund invests on TB and HIV, *9.2 million people* were put on antiretroviral treatment for HIV so far, and *15.1 million people* have received TB treatment.

In the case of Tuberculosis, the Global Fund is the largest contributor, providing *three-quarters of all international financing for TB*, focusing on countries with the highest disease burden and with the highest proportion of affected populations.

Figure 2.



In addition to supporting disease specific Programs, the organization considers building *resilient and sustainable systems for health* critically important to end HIV, TB and malaria as epidemics, and to create substantial positive effects on the overall systems for health. Therefore, *40%* of Global Fund investments go toward building resilient and sustainable systems for health.

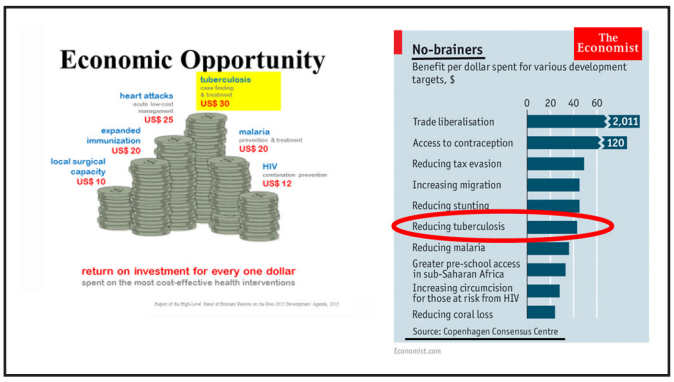
Additionally, the Global Fund supports countries in expanding programs that *remove human rights- and gender-related obstacles to health care* so that everyone can access the health services they need. To specifically address the inequalities affecting women and girls, its investments have increased significantly in the past six years, with about *60%* of the organization's total investments now directed to these groups.

The Ebola outbreak in West Africa and the increasing global crisis of refugees and displaced people have revealed unique problems in providing access to health care in challenging operating environments. *Challenging operating environments* account for *one-third* of the global disease burden for HIV, TB and malaria and one-third of Global Fund investments.

Finally, The Global Fund plays a catalytic role in spurring greater investment. The proportion of investments in health that come from domestic financing is growing each year (more than half of funding for HIV, more than three-quarters for TB and around a quarter for malaria), and this financing requirement is an effective way to work with governments to stimulate domestic investments in health. To date, countries have committed an additional *US$6 billion* to their health programs for 2015-2017 – a 41% increase in domestic financing for health.

Lastly, it has to be reminded that investing in these diseases has a concrete impact not only on the patients affected by them, but also in terms of economic return. And this is especially relevant for TB.

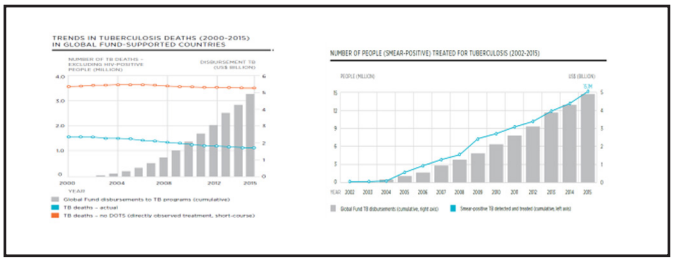
Figure 3.



Progresses and challenges in The Global Fund support to TB, TB/HIV and MDR-TB.

Over the last 15 years the number of *deaths from TB* declined *31%* in countries where the Global Fund invests (excluded deaths among co-infection of HIV and TB). And if we consider only the 2015, it is estimated that the number of deaths would have been more than *three times higher* in the absence of interventions. This decline was supported by an increase in the number of TB cases detected and treated over the past decade. On the other side, the number of TB cases averted has been growing each year, with a substantial increase in funding for TB prevention, diagnosis and treatment.

Figure 4.



Despite steady yearly declines in the number of new infections and deaths, TB remains a stubborn and deadly challenge; in 2015, TB surpassed HIV as the leading killer among infectious diseases (largely due to faster progress against HIV, which lowered HIV-related deaths in comparison with TB).

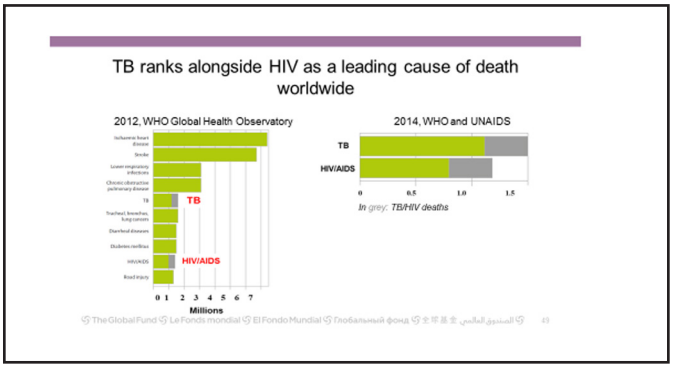
In 2000, *AIDS* seemed unstoppable, but since then, enormous progresses have been done. After peaking in 2005, the number of HIV-related deaths has declined by 45% in countries where the Global Fund invests. Here programs provide ARV therapy for 9.2 million people – more than half the global total of people on treatment.

Globally, as a result of the collective efforts of all governments and partners, *46%* of all people living with HIV now have *access to ARV therapy* – a striking increase from 2.7 percent in 2000 and just 6.8 percent in 2005.

A leading factor in expanding access to treatment is reducing prices for ARVs. The Global Fund's pooled procurement mechanism delivers HIV drugs more effectively and reliably and at sharply lower cost. In 2000, a one-year supply of ARVs cost more than US$10,000. It can now cost as low as US$94.

TB/HIV co-infection is an enduring problem, with HIV infection complicating treatment and care for TB patients, and TB the most frequent primary clinical diagnoses and the commonest cause of death among HIV patients. As of March 2016, forty single TB/HIV concept notes from 39 countries were submitted to the Global Fund. In fact, to encourage country dialogue among TB and HIV programs, stakeholders and communities affected by the two diseases, the Global Fund required countries with high TB and HIV burdens to develop TB/HIV joints applications to request funds. The aim is to achieve better coordination and collaboration in planning and implementing activities that address TB and HIV communities, to take advantage of all the possible synergies and opportunities for efficiencies and for better results, and for larger impact. However, moving from theory to practice may be tough, and sometimes the implementation on the ground of TB/HIV joint interventions is challenging. Although most of the so-called TB/HIV collaborative activities recommended by WHO – World Health Organization have shown great progresses in the last years, IPT –isoniazid preventive therapy is greatly lagging behind. However, overall, the single concept note has enabled intensified dialogue between stakeholders of the two respective programs and a more comprehensive review of applications, with focus on leverages in health and community systems strengthening for TB and HIV.

Figure 5.

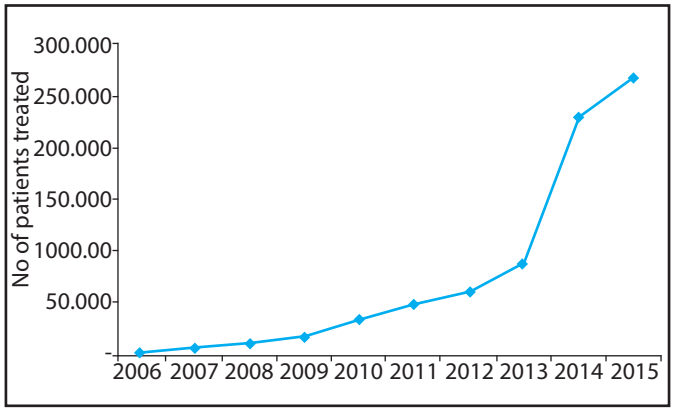


Multidrug-resistant TB (MDR-TB) has received increasing attention as it grows into a potentially catastrophic threat to public health, especially in Eastern Europe, some countries in Asia and

parts of Southern Africa. MDR-TB and XDR-TB (extensively resistant TB) increase the cost, complexity and length of treatment.

MDR-TB cases treated by GF-supported programs increased *from 64,000 in 2012 to 270,000 in 2015*, and there has been an *increasing trend of funding available for MDR-TB* through allocation, reprogramming and savings (from 9% in 2008 to over 30% in 2014).

Figure 6. Cumulative No of MDR-TB patients treated by GF-supported programs.



Global Fund grants support the procurement and supply of *second-line anti-TB drugs and ancillary medicines* required for quality clinical management of MDR-TB patients.

Several countries have included funding requests for introduction of *new drugs such Bedaquiline and Delamanid* - including support for monitoring drug safety and capacity building .

The GF has financed introduction of *MDR-TB short regimens* as part of operational research in several countries, and the investments have contributed to generating additional evidence to inform the recent WHO recommendation (May 2016). The majority of countries currently are reprogramming their grants/savings to introduce and/or scale-up these shorter regimen following the new WHO recommendation. These shorter regimens cost less half the cost of the conventional treatment and are expected to enable improved outcomes (over 80% of successful outcomes in the cohorts of patients on short regimens so far).

In the last few years Global Fund grants have largely supported introduction and *scale-up of Xpert MTB/RIF* and other molecular diagnostic tests. However, Xpert implementation and complete laboratory expansion plan results sometimes challenging, with underused machines, restrictive algorithms and weak sample transport systems. Additionally, in various countries is challenging maintaining aligned diagnostic and treatment capacities, and MDR-TB outcomes are still poor.

The GF grants have also contributed to the *reform model of treatment of TB / MDR-TB*, from hospital-based to outpatient treatment to ambulatory and patient-centered treatment, and have also supported cross-sector collaboration through private sector engagement of other care providers, such as *public-private mix* for MDR-TB cases. In some countries, especially in Asia, where the majority of TB and MDR-TB patients may initially access services from private providers, this is especially relevant to improve case detection and management.

To ensure that patients receive adequate and appropriate support during diagnosis and treatment, and in order to avoid catastrophic costs to patients and their families, *"enabler" packages are also funded through the grants*. These include information/education, psychological support, and material support to cover transportation costs, nutritional needs, and other services.

In addition to funding technical assistance through the grants allocated to the countries, GF provides support for all *regional Green Light Committees* (rGLCs) to provide *technical support* to the countries.

Finally, *Drug-resistance surveys* are funded in an increasing number of countries to generate data and evidence for planning purposes, as well as for designing country-specific regimens and for monitoring trends of MDR-TB to guide high-impact investments.

Lastly, special funding are provided to *address cross-border issues* including MDR-TB response among migrant workers, TB among mining communities in Southern Africa region, Supranational laboratory in East and Southern Africa and TB/MDR-TB among Syrian refugee and migrants.

Future Scenario

The Global Fund seek to mobilize US$13 billion for the Fifth Replenishment (for the period 2017-2019). Analysis show that this level of investment, combined with significant increases in domestic financing, with other external funding remaining steady, and with advances in implementation, would reach 80 percent of the total need projected by partners.

Overall, a US$13 billion (13.000 millions) contribution for the Fifth Replenishment would:

- Save up to 8 million lives through programs supported by the GF, leading to 30-32 million lives saved cumulatively by 2020;
- Avert up to 300 million new infections across the three diseases;
- Allow the GF to make substantial contributions towards building resilient and sustainable systems for health;
- Support partners in domestic investment of US$41 billion toward the three diseases;

– Support strengthened responses for women and girls, key populations and human rights;
– Lead to broad economic gains of up to US$290 billion over the coming years, based on estimates on the return on investment for implementing each of the global plans. These are based on the economic value of better health and a more productive society by trying to capture productivity and consumption gains, including through household savings, and calculating that each person who goes on lifesaving treatment is a potential contributor to the economic health of a community.

Actually, at the fifth replenishment held in Montreal on September 2016, a donors' pledge of approximately 13 Billion has been achieved.

There is no obstacle too great, nor too difficult, which cannot be overcome by collective action and persistence. That lesson is especially manifest in global efforts to end HIV, TB and malaria. Good results have become clearly visible in the last years, but a lot of work still needs to be done to achieve the ambitious targets set by WHO, STOP TB and Unaids to end the epidemics.

Therefore, continued and stepped-up commitment of stakeholders to addressing the interlinked epidemics more effectively remains essential.

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