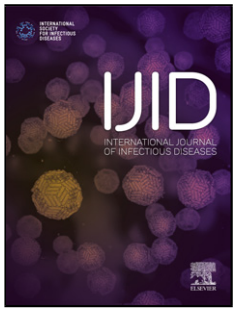

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Time to embrace access programmes for medicines: Lessons from the South African flucytosine access programme

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Highlights

- Market failure has meant that flucytosine, a potentially lifesaving medicine for the treatment of cryptococcal meningitis is not accessible in African treatment programmes
- A recently established access programme has allowed for wide scale public sector access to flucytosine in South Africa
- We advocate that access programmes for medicines be utilized more widely as part of the solution to addressing market failure

Abstract

Background

Cryptococcal Meningitis (CM) is estimated to cause 181,000 deaths annually; with the majority occurring in Sub Saharan Africa. Flucytosine is recommended by the World Health Organization as part of the treatment for CM. Widespread use of flucytosine could reduce mortality in hospital by as much as 40% compared to the standard of care, yet due to market failure quality assured flucytosine remains unregistered and largely inaccessible throughout Africa.

Methods

The recently established South African flucytosine clinical access programme is an attempt to address market failure which led to a lack of public-sector access to flucytosine for cryptococcal meningitis, by making the medicine freely available to tertiary hospitals in South Africa.

Results

Between November 2018 and September 2019, 327 CM patients received flucytosine through this programme, with efforts to support sustainable national scale up presently ongoing. We describe why this programme was needed, its catalytic potential, what is still required to ensure widespread access to flucytosine, and observation from this experience that may have wider relevance.

Conclusions

The South African Flucytosine Access Programme illustrates how access programmes may be one part of the solution to addressing the vicious cycle of perceived low demand, limiting manufacturer interest in specific product markets.

Keywords: HIV; Access; AIDS: cryptococcal meningitis; Flucytosine; South Africa; AIDS

mortality: advanced HIV disease; Ahd

The transition from phase 3 clinical trials demonstrating efficacy of a medicine to widespread access in routine-care settings can be slow and tortuous, particularly for neglected diseases such as cryptococcal meningitis (1). Here we outline the usefulness of clinical access programmes, one mechanism to bridge this period. The recently established South African flucytosine clinical access programme is an attempt to address market failure that led to a lack of public-sector access to flucytosine for cryptococcal meningitis. Initially, Médecins Sans Frontières (MSF) procured flucytosine with the support of South Africa's National Department of Health, under an import exemption (in terms of Section 21 of the Medicines and Related Substances Act, 101 of 1965) in order to supply this unregistered medicine to tertiary public-sector hospitals in the country. We describe why this programme was needed, its catalytic potential, what is still required to ensure widespread access to flucytosine, and observation from this experience that may have wider relevance.

Flucytosine, in combination with amphotericin B, significantly reduces mortality among people living with human immunodeficiency virus (HIV) infection who suffer from cryptococcal meningitis, it has a favorable safety profile and allows for the duration of amphotericin B infusion to be decreased, thus reducing toxicity.(2) Quality assured flucytosine is however not registered in any country in Africa, the very place where it would be of most benefit (3). In sub-Saharan Africa, this medicine is commonly substituted by fluconazole which is associated with inferior clinical outcomes (2). Those who do not tolerate amphotericin B may receive even less effective fluconazole monotherapy. Flucytosine, developed in 1957, has been off patent for decades, yet the cost in the US and other parts of the world has remained extraordinarily high because of manufacturer monopoly pricing (4), at around 25,000 US dollars per 2-week treatment course (Micromedex Redbook). Manufacturers seem to perceive the market for flucytosine elsewhere as unattractive while national departments of health have avoided its inclusion in guidelines and on essential medicines lists until registration is completed, the latter

a lengthy and complicated process in many countries. This has meant that most people with cryptococcal meningitis continue to receive sub-standard therapy or no therapy at all, hindering efforts to reduce the estimated 140,000 annual cryptococcal meningitis deaths in sub-Saharan Africa (5).

Market failure with respect to flucytosine principally relates to issues at the following levels: i) At government level, this medicine appears to have been viewed as unaffordable (6). This may have been exacerbated by the fact that manufacturers have not always been transparent on pricing (author's personal efforts to obtain pricing information) nor forthcoming with a reduced access price for the public sector (7).

ii) On the manufacturer's side, the profit margins from low- and middle-income countries (LMICs) may not be perceived as substantial enough to justify investing the time and resources needed to file for registration and scale up manufacturing and distribution. This is in contrast to the situation in North America, where the product is registered and available, albeit at a very high price.

In addition, manufacturers have complained of poor demand, however this can only be generated if the product is registered and appears in guidelines in respective countries, a catch-22 situation.

iii) Providers are unfamiliar with the medicine so are less likely to seek to use it, even if available prior to registration off license. Flucytosine can be obtained in South Africa under the Section 21 exemption system.

This has resulted in a vicious cycle where limited interest from end-users (clinicians treating people with HIV-associated cryptococcal meningitis) has led to weak and unarticulated demands from government, which in turn has contributed to the perception of the market as unattractive, thus severely limiting patient access (8).

The publication of the Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa (ACTA) trial results (2)(9) has greatly strengthened calls to increase access to this medicine, with mortality reductions in the region of 40% reported at 10 weeks reported with

the use of flucytosine (versus fluconazole) in induction therapy in combination with amphotericin B for cryptococcal meningitis. The magnitude of benefit, and strength of evidence has helped to shift the argument for flucytosine access to a humanitarian, as well as a scientific imperative.

The South African flucytosine clinical access programme was established in the second half of 2018 by Médecins Sans Frontières (MSF) in conjunction with a range of key South African clinicians through the Southern African HIV Clinicians Society. It sought to ensure flucytosine supply to tertiary hospitals in South Africa, until such time as the medicine became available throughout the country. This has contributed to some modest successes. Between 1st November 2018 and 1st September 2019, we have collected data on 327 patients treated within this programme. In-hospital mortality observed among cryptococcal meningitis patients treated during this period at supported sites was 25% during admission, compared to 36% mortality observed at the same sites prior to flucytosine introduction (10). While future more definitive comparisons will require adjustment for confounding; we provide this data to illustrate outcomes achievable with flucytosine in routine use.

Along with this limited access, the South African National Essential Medicines List Adult Hospital Level Medication Review Process recently concluded that flucytosine should form part of the preferred regimen for cryptococcal meningitis treatment, “pending South African Health Products Regulatory Authority (SAHPRA) registration with a reduction in price” (11).

The situation with regard to flucytosine access remains precarious. While industry interest in the medicine is increasing, the medicine remains unregistered and this modest programme established in South Africa appears to have exhausted all stock that the principal manufacturer (Mylan) states can be provided in the short term. This programme may be thought of as a transitional access mechanism, having the potential both to facilitate wider access (the humanitarian perspective) as well as to produce evidence of a market and of the medicine’s importance to public health.

The role of civil society

There are currently many other medicines of public health importance in LMICs with good evidence of efficacy but poor accessibility. These include directly acting antivirals (DAAs) for hepatitis C, delamanid for drug-resistant TB, and rifabutin for TB infection in patients with HIV.

In the early era of the AIDS epidemic, the unacceptability of poor access to ART was prominent in the public discourse and led to vocal and effective civil society mobilization to demand fair access. Around the turn of the century the treatment action campaign (TAC) and others mounted an effective "defiance campaign", importing, alongside antiretrovirals, generic fluconazole at a time when price the registered originator version was a major impediment to accessing it for use in cryptococcal meningitis, with these efforts helping to catalyze wide systemic change (12). Such pressure would be useful now in the case of flucytosine and other essential but unavailable medicines, but is not currently seen in as vocal or impactful form.

The role of donors

We call upon funders to consider wider use of transitional access mechanisms such as clinical access programmes, given that they have the potential to provide data on the effectiveness and benefits of new regimens in real-world settings, establish the role of new medicines in high prevalence and resource-limited regions, create familiarity with use of the medicine among health care workers, and provide much needed access to patients while awaiting registration and routine use. Such programmes also bring wider attention with the potential to promote meaningful dialogue between all vested stakeholders including civil society.

Through these activities it may be possible to demonstrate the presence of a market to manufacturers, while supporting earlier registration by providing locally-derived data to relevant medicines regulators. By institutionalizing the role of such programmes and mechanisms, expedited access to medicines of public health importance in LMIC settings can become the norm rather than the exception. However, this will require a willingness to think outside typical paradigms, where Non Governmental Organisations (NGOs) seek simply to help government reach predetermined objectives, and other stakeholders passively await the availability of new medicines. Donors should recognize and maximally leverage their relative flexibility in this arena.

Potential pitfalls

We see such initiatives as distinct from manufacturer-sponsored and/or led donation programmes. Such programmes should be careful to balance the benefit to public health against the potential to distort or hinder market growth and in so doing, hampering longer-term access.

Access programmes should not be viewed as an alternative to, but rather as leading to, the ultimate aim of sustainable widespread public-sector access to medicines that have received regulatory approval and whose use will ultimately be integrated into routine programmes funded by national departments of health. Ensuring this transition necessitates close collaboration throughout with departments of health throughout the process.

While such programmes may appear “light” in comparison to a trial, they do require careful coordination around the logistics of supply, pharmacovigilance reporting and follow up with implementing sites; practical support from an organization with an implementation presence, such MSF, may be useful in this regard.

Summary

The South African flucytosine access programme illustrates how access programmes may be one part of the solution to addressing the vicious cycle of perceived low demand, limiting manufacturer interest in specific product markets.

In the case of flucytosine, there remains an urgent need for generic manufacturers to file for registration and for the medicine to be included in national level guidelines, which will facilitate its use in the countries where it will have the most public health impact. This requires continued sustained work from governments, civil society and other non-governmental actors.

UNITAID will provide funds through a Clinton Health Access Initiative (CHAI) grant to ensure the continuation of the South African flucytosine clinical access programme. We hope that this will help encourage additional future investment in programmes to address market failure for key commodities needed in LMICs. We hope this experience will help such mechanisms to be more

widely acknowledged as having a legitimate space in the medicine development and access continuum, particularly where the human costs of delayed access are so high.

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